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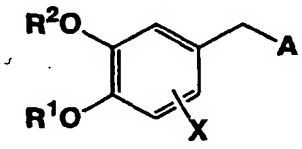
(54) PURINE DERIVATIVES AND MEDICINE CONTAINING THE SAME AS THE ACTIVE INGREDIENT

(57) Purine derivatives represented by the following formula and salts thereof:



(I)

wherein R^1 represents a C_1-C_4 alkyl group or difluoromethyl group; R^2 represents tetrahydrofuranyl group, a C_1-C_7 alkyl group and the like; X represents hydrogen atom, a halogen atom or nitro group; and A represents a group represented by the following formula:

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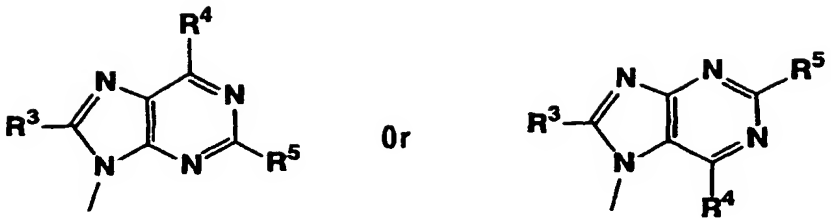


wherein R^3 represents hydrogen atom, a halogen atom and the like; R^4 and R^5 represent hydrogen atom, a halogen atom, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group and the like, which are useful as active ingredients of medicaments such as antiasthmatic agents.

Description

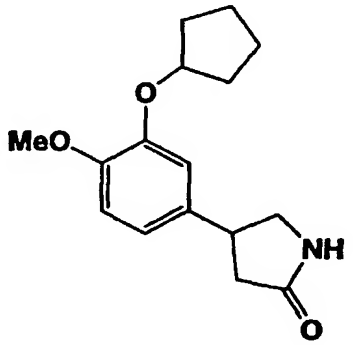
Technical Field

[0001] The present invention relates to novel purine derivatives. More precisely, it relates to purine derivatives having inhibitory activity against phosphodiesterase IV. The present invention also relates to synthetic intermediates for the preparation of said novel purine derivatives.

Background Art

[0002] Cyclic AMP (cAMP) is an important second messenger which is involved in relaxation of respiratory tract smooth muscles and control of inflammatory cells, and the messenger is decomposed by phosphodiesterase (hereinafter abbreviated as "PDE" in the specification) to be converted into inactive 5'-AMP. Therefore, it is believed that suppression of the decomposition of cAMP by PDE may increase the concentration of cAMP, thereby bronchodilatation and anti-inflammatory action can be achieved. For this reason, PDE inhibitors having inhibitory action against the decomposition of cAMP have been focused as medicaments for the treatment of asthma. In addition, five PDE isozymes (PDE I, II, III, IV and V) have recently been isolated, and their specific tissue distributions have been revealed (Adv. Second Messenger Phosphoprotein Res., 22, 1 (1988); Trends Pharm., Sci., 11, 150 (1990)).

[0003] Among inhibitors for these isozymes, in particular, inhibitors specific for PDE IV have been suggested to be possibly useful for the treatment of asthma (Thorax 46, 512 (1991)). As a compound having specific inhibitory activity against PDE IV, for example, the compound disclosed in Japanese Patent Unexamined Publication (Kokai) No. 50-157360/1975 (Rolipram) has been known.



[0004] Although various compounds have been known as PDE IV inhibitors (for example, compounds disclosed in Japanese Patent Unexamined Publication (Kokai) No. 4-253945/1992, International Patent Publication in Japanese (Kohyo) Nos. 6-504782/1994, 7-504442/1995, 8-501318/1996 and 9-500376/1997 and so forth), they have not been used clinically so far, and development of novel compounds having PDE IV inhibitory activity has been desired.

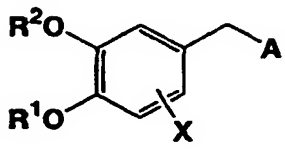
Disclosure of the Invention

[0005] An object of the present invention is to provide a novel compound having specific inhibitory activity against PDE IV, of which possible usefulness for treatment of asthma has been suggested. Another object of the present invention is to provide a medicament comprising a compound that has the aforementioned characteristic as an active ingredient. A further object of the present invention is to provide a synthetic intermediate useful for efficient preparation of the aforementioned compound.

[0006] The inventors of the present invention earnestly conducted researches to achieve the foregoing objects. As a result, they found that particular class of purine derivatives represented by the following formula had excellent inhibitory activity against PDE IV. They also found that these compounds were useful as active ingredients of medicaments, and they were extremely useful as, for example, as active ingredients of antiasthmatic agents. The present invention was achieved on the basis of these findings.

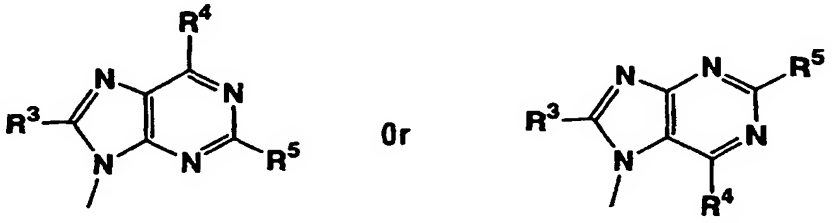
[0007] The present invention thus provides purine derivatives represented by the following formula (I), salts thereof,

or N-oxides thereof, or hydrates thereof or solvates thereof:



(I)

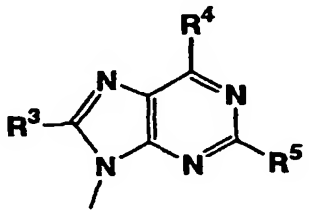
wherein R^1 represents a C_1-C_4 alkyl group or difluoromethyl group; R^2 represents tetrahydrofuranyl group, a C_1-C_7 alkyl group, a C_1-C_7 haloalkyl group, a C_2-C_7 alkenyl group, bicyclo[2,2,1]hept-2-yl group, or a C_3-C_8 cycloalkyl group; X represents hydrogen atom, a halogen atom, or nitro group; and A represents a group represented by the following formula:



wherein R^3 represents hydrogen atom, a halogen atom, hydroxyl group, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, amino group, a C_1-C_4 alkylamino group, or a C_2-C_8 dialkylamino group; R^4 and R^5 each independently represent hydrogen atom, a halogen atom, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, amino group, a C_1-C_4 alkylamino group, pyrrolidinyl group, morpholino group, a C_2-C_8 dialkylamino group, or a group represented by -Y-$(CH_2)_n$-B {Y represents -O-, -S-, -NHCO-, or -N(R^6)- (R^6 represents hydrogen atom or a C_1-C_4 alkyl group), n represents an integer of from 0 to 4, and B represents a phenyl group, a naphthyl group, or a heterocyclic residue, each of which may be substituted}, provided that either R^4 or R^5 represents -Y-$(CH_2)_n$-B {Y represents -O-, -S-, -NHCO-, or -N(R^6)- (R^6 represents hydrogen atom or a C_1-C_4 alkyl group)} when X represents hydrogen atom,, and

(i) n represents an integer of from 0 to 4, and B represents a phenyl group, a naphthyl group, or a heterocyclic residue, each of which may be substituted when Y represents -O-, -S-, or -NHCO-, or
(ii) n represents an integer of from 1 to 4, and B represents a heterocyclic residue when Y represents -N(R^6)-.

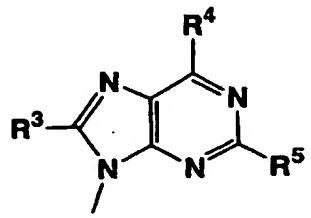
[0008] According to preferred embodiments of the present invention, there are provided the aforementioned purine derivatives, salts thereof, or N-oxides thereof, or hydrates thereof or solvates thereof, wherein A is a group represented by the following formula:



wherein R^3 is hydrogen atom, a halogen atom, hydroxyl group, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, amino group, a C_1-C_4 alkylamino group or a C_2-C_8 dialkylamino group; one of R^4 and R^5 is hydrogen atom, a halogen atom, a C_1-C_4

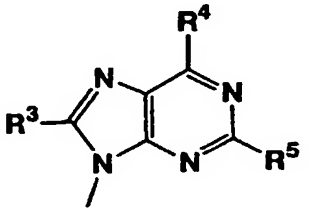
alkyl group, a C_1-C_4 alkoxyl group, amino group, a C_1-C_4 alkylamino group, pyrrolidinyl group, morpholino group, or a C_2-C_8 dialkylamino group, and the other is -Y-$(CH_2)_n$-B (Y is -O-, -S-, -NHCO-, or -N(R^6)- (R^6 represents hydrogen atom or a C_1-C_4 alkyl group), n is an integer of from 0 to 4, and B represents a phenyl group, a naphthyl group, or a heterocyclic residue, each of which may be substituted);

the aforementioned purine derivatives, salts thereof, or N-oxides thereof, or hydrates thereof or solvates thereof, wherein R^1 is a C_1-C_4 alkyl group; R^2 is tetrahydrofuranyl group, a C_1-C_6 alkyl group, a C_1-C_3 haloalkyl group or a C_3-C_8 cycloalkyl group, and A is a group represented by the following formula:



wherein R_3 is hydrogen atom, a halogen atom, hydroxyl group, a C_1-C_4 alkyl group, or a C_1-C_4 alkoxyl group; R_4 is hydrogen atom, a halogen atom, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, a C_1-C_4 alkylamino group, or a C_2-C_8 dialkylamino group, R^5 is -Y-$(CH_2)_n$-B (Y is -O-, -S-, or -NHCO-, n is an integer of from 1 to 4, and B represents a heterocyclic residue which may be substituted); and

the aforementioned purine derivatives, salts thereof, or N-oxides thereof, or hydrates thereof or solvates thereof, wherein R^1 is a C_1-C_3 alkyl group; R^2 is a C_3-C_8 cycloalkyl group, and A is a group represented by the following formula:

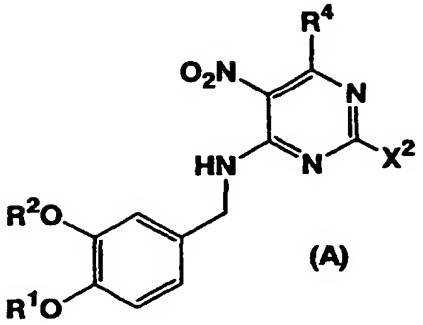


wherein R^3 is hydrogen atom, a C_1-C_3 alkyl group, or a C_1-C_3 alkoxyl group; R^4 is a C_1-C_3 alkyl group, a C_1-C_3 alkoxyl group or a C_1-C_3 alkylamino group; R^5 is -Y-$(CH_2)_n$-B (Y is -O-, n is an integer of from 1 to 4, and B is a heterocyclic residue which may be substituted).

[0009] According to another aspect of the present invention, medicaments are provided which contain a substance selected from the group consisting of the aforementioned purine derivatives, salts thereof, and N-oxide compounds thereof, and hydrates thereof and solvates thereof as an active ingredient. These medicaments are preferably provided as pharmaceutical compositions which contain the aforementioned active ingredient and an additive for pharmaceutical preparation, and they can be used as, for example, antiasthmatic agents for preventive and/or therapeutic treatment of asthma.

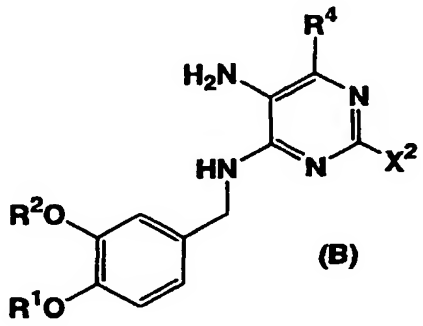
[0010] According to further aspects of the present invention, there are provided use of a substance selected from the group consisting of the aforementioned purine derivatives, salts thereof, and N-oxide compounds thereof, and hydrates thereof and solvates thereof for the manufacture of the aforementioned medicaments; methods for preventive and/or therapeutic treatment of asthma which comprise the step of administering an effective amount of a substance selected from the group consisting of the aforementioned purine derivatives, salts thereof, and N-oxide compounds thereof, and hydrates thereof and solvates thereof to a mammal including human; and phosphodiesterase IV inhibitors which comprise a substance selected from the group consisting of the aforementioned purine derivatives, salts thereof, and N-oxide compounds thereof, and hydrates thereof and solvates thereof.

[0011] According to further aspects of the present invention, there are provided compounds represented by the following formula (A):



(A)

wherein R^1 represents a C_1-C_4 alkyl group or difluoromethyl group; R^2 represents tetrahydrofuranyl group, a C_1-C_7 alkyl group, a C_1-C_7 haloalkyl group, a C_2-C_7 alkenyl group, bicyclo[2,2,1]hept-2-yl group or a C_3-C_8 cycloalkyl group; R^4 represents hydrogen atom, a halogen atom, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, amino group, a C_1-C_4 alkylamino group, pyrrolidinyl group, morpholino group, a C_2-C_8 dialkylamino group or -Y-$(CH_2)_n$-B {Y represents -O-, -S-, -NHCO-, or -N(R^6)- (R^6 represents hydrogen atom or a C_1-C_4 alkyl group), n represents an integer of from 0 to 4, B represents a phenyl group, a naphthyl group, or a heterocyclic residue, each of which may be substituted, and X^2 represents a halogen atom, and
compounds represented by the following formula (B):



(B)

wherein R^1 represents a C_1-C_4 alkyl group or difluoromethyl group; R^2 represents tetrahydrofuranyl group, a C_1-C_7 alkyl group, a C_1-C_7 haloalkyl group, a C_2-C_7 alkenyl group, bicyclo[2,2,1]hept-2-yl group, or a C_3-C_8 cycloalkyl group; R^4 represents hydrogen atom, a halogen atom, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, amino group, a C_1-C_4 alkylamino group, pyrrolidinyl group, morpholino group, a C_2-C_8 dialkylamino group, or -Y-$(CH_2)_n$-B {Y represents -O-, -S-, -NHCO-, or -N(R^6)- (R^6 represents hydrogen atom or a C_1-C_4 alkyl group), n represents an integer of from 0 to 4, B represents a phenyl group, a naphthyl group, or a heterocyclic residue, each of which may be substituted, and X^2 represents a halogen atom. These compounds are useful as synthetic intermediates for preparation of the compounds represented by the aforementioned formula (I).

[0012] According to preferred embodiments of the synthetic intermediates represented by the formula (A) or (B), there are provided those wherein R^1 is a C_1-C_4 alkyl group, R^2 is tetrahydrofuranyl group, a C_1-C_6 alkyl group, a C_1-C_3 haloalkyl group, or a C_3-C_8 cycloalkyl group, R^4 is hydrogen atom, a halogen atom, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, a C_1-C_4 alkylamino group or a C_2-C_8 dialkylamino group.

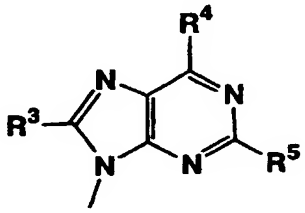
Best Mode for Carrying out the Invention

[0013] R^1 represents a linear or branched C_1-C_4 alkyl group (methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, t-butyl group and the like), or difluoromethyl group. R^1 preferably represents a C_1-C_4 alkyl group, more preferably a C_1-C_3 alkyl group, further preferably methyl group or ethyl group, and

most preferably methyl group.

[0014] R^2 represents tetrahydrofuranyl group, a C_1-C_7 linear or branched alkyl group (methyl group R^2 represents, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, t-butyl group, n-pentyl group, 1,2-dimethylpropyl group, 1,1-dimethylpropyl group, n-hexyl group, 1-methylpentyl group, 2-methylpentyl group, 3-methylpentyl group, 4-methylpentyl group, 1,1-dimethylbutyl group, 2,2-dimethylbutyl group, 3,3-dimethylbutyl group, 1,2-dimethylbutyl group, 1,3-dimethylbutyl group, 1,2,2-trimethylpropyl group, heptyl group, 5-methylhexyl group, 2,2-dimethylpentyl group, 3,3-dimethylpentyl group, 4,4-dimethylpentyl group, 1,2-dimethylpentyl group, 1,3-dimethylpentyl group, 1,4-dimethylpentyl group, 1,2,3-trimethylbutyl group, 1,1,2-trimethylbutyl group, 1,1,3-trimethylbutyl group and the like), a C_1-C_7 haloalkyl group (chloromethyl group, bromomethyl group, dichloromethyl group, 1-chloroethyl group, 2-chloroethyl group, 3-chloropropyl group, 3-chlorobutyl group, 5-chloropentyl group, 6-chlorohexyl group, difluoromethyl group, trifluoromethyl group and the like), a C_2-C_7 alkenyl group (vinyl group, allyl group, 2-propenyl group, isopropenyl group, 3-butenyl group, 4-pentenyl group, 5-hexenyl group and the like), bicyclo[2,2,1]hept-2-yl group, or a C_3-C_8 cycloalkyl group (cyclopropyl group, cyclobutyl group, cyclopentyl group, cyclohexyl group, cycloheptyl group and the like). R^2 preferably represents tetrahydrofuranyl group, a C_1-C_6 alkyl group, a C_1-C_3 haloalkyl group, or a C_3-C_8 cycloalkyl group, more preferably a C_3-C_8 cycloalkyl group, further preferably a C_4-C_6 cycloalkyl group, and most preferably cyclopentyl group.

[0015] X represents hydrogen atom, a halogen atom (when a halogen is referred to in the specification, the halogen may be any of fluorine, chlorine, bromine, and iodine), or nitro group, preferably hydrogen atom. As symbol "A", a group represented by the following formula is preferred.



[0016] In the above formula, R^3 represents hydrogen atom, a halogen atom, hydroxyl group, a linear or branched C_1-C_4 alkyl group (methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, t-butyl group and the like), a linear or branched C_1-C_4 alkoxyl group (methoxy group, isopropoxy group, butoxy group and the like), amino group, a linear or branched C_1-C_4 alkylamino group (methylamino group, n-propylamino group, isopropylamino group, butylamino group and the like) or a linear or branched C_2-C_8 dialkylamino group (dimethyl amino group, diethylamino group, dipropylamino group, dibutylamino group and the like). R_3 preferably represents hydrogen atom, a halogen atom, hydroxyl group, a linear or branched C_1-C_4 alkyl group, a C_1-C_4 linear or branched alkoxyl group, more preferably hydrogen atom, a C_1-C_3 alkyl group or a C_1-C_3 alkoxyl group.

[0017] In the aforementioned formula, R^4 and R^5 each independently represent hydrogen atom, halogen atom, a linear or branched C_1-C_4 alkyl group (methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, t-butyl group and the like), a linear or branched C_1-C_4 alkoxyl group (methoxy group, isopropoxy group, butoxy group and the like), amino group, a linear or branched C_1-C_4 alkylamino group (methylamino group, n-propylamino group, isopropylamino group, butylamino group and the like), pyrrolidinyl group, morpholino group, a linear or branched C_2-C_8 dialkylamino groups (dimethylamino group, diethylamino group, dipropylamino group, dibutylamino group and the like) or -Y-$(CH_2)_n$-B {Y is -O-, -S-, -NHCO-, or -N(R^6)- (R^6 is hydrogen atom or a linear or branched C_1-C_4 alkyl group (methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, t-butyl group and the like), and Y is preferably -O-)}. Symbol "n" represents an integer of from 0 to 4, preferably an integer of from 1 to 3.

[0018] B represents a phenyl group, a naphthyl group, or a heterocyclic residue. Each of these groups may have, on their rings, one or more substituents selected from the group consisting of a halogen atom, a linear or branched C_1-C_4 alkyl groups (methyl group, ethyl group, n-propyl group, isopropyl group, n-butyl group, isobutyl group, sec-butyl group, t-butyl group and the like), a C_1-C_4 haloalkyl group (chloromethyl group, bromomethyl group, dichloromethyl group, 1-chloroethyl group, 2-chloroethyl group, 3-chloropropyl group, 4-chlorobutyl group, difluoromethyl group, trifluoromethyl group and the like), a linear or branched C_1-C_4 alkoxyl group (methoxy group, isopropoxy group, butoxy group and the like), a linear or branched C_1-C_4 haloalkoxyl group (trifluoromethoxy group, difluoromethoxy group, 2,2,2-trifluoroethoxy group, 3-chloropropoxy group and the like), cyano group, nitro group, amino group, hydroxy group, carboxy

group, a C_1-C_4 acyl groups (formyl group, acetyl group, propionyl group and the like), a C_2-C_4 alkoxycarbonyl group (methoxycarbonyl group, ethoxycarbonyl group and the like), a linear or branched C_1-C_4 alkylamino group (methylamino group, isopropylamino group, butylamino group etc.), and a linear or branched C_2-C_6 dialkylamino group (dimethylamino group, diethylamino group and the like), preferably one or more substituents selected from the group consisting of a halogen atom, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, a C_1-C_4 haloalkoxyl group, carboxy group, and a C_2-C_4 alkoxycarbonyl group.

[0019] As the heterocyclic residue, a heterocyclic residue having 1 to 5 hetero atoms selected from oxygen atom, sulfur atom and nitrogen atom and having 5 to 10 ring-constituting atoms may be used, such as thienyl group, furyl group, pyrrolyl group, imidazolyl group, pyrazolyl group, triazolyl group, tetrazolyl group, oxazolyl group, isooxazolyl group, thiazolyl group, isothiazolyl group, pyrrolidinyl group pyridyl group, pyridazinyl group, pyrazinyl group, pyrimidinyl group, triazinyl group, piperidyl group, piperidino group, morpholinyl group, morpholino group, piperazinyl group, benzimidazolyl group, indolyl group, quinolyl group, naphthylidinyl group, quinazolinyl group and the like, preferably thienyl group, furyl group, pyrrolyl group, imidazolyl group, pyrazolyl group, pyridyl group, pyridazinyl group, pyrazinyl group, pyrimidinyl group, triazinyl group, piperidyl group, piperidino group, morpholinyl group, morpholino group, piperazinyl group, benzimidazolyl group and the like, more preferably a 6-membered heterocyclic residue having one or two nitrogen atoms as the hetero atom(s), for example, pyridyl group, pyridazinyl group, pyrazinyl group, pyrimidinyl group, triazinyl group, piperidyl group, piperidino group, morpholinyl group, morpholino group, piperazinyl group and the like. B represents a heterocyclic residue which may be substituted, and most preferably an unsubstituted heterocyclic residue.

[0020] As for R^4 and R^5, R^4 preferably represents hydrogen atom, a halogen atom, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, a C_1-C_4 alkylamino group, or a C_2-C_8 dialkylamino group, more preferably a C_1-C_3 alkyl group, a C_1-C_3 alkoxyl group, or a C_1-C_3 alkylamino group, and R_5 represents - Y-$(CH_2)_n$-B (Y, n, and B have the same meanings as already defined above).

[0021] When X represents hydrogen atom, either of R^4 or R^5 represents -Y-$(CH_2)_n$-B. In this case, Y represents -O-, -S-, -NHCO-, or -$N(R^6)$- (R^6 represents hydrogen atom or a C_1-C_4 alkyl group), and (i) when Y represents -O-, -S-, or -NHCO-, n represents an integer of from 0 to 4, and B represents a phenyl group, a naphthyl group, or a heterocyclic residue, each of which may be substituted, or (ii) when Y represents -$N(R^6)$-, n represents an integer of from 1 to 4, and B represents a heterocyclic residue.

[0022] When R^4 or R^5 in the compounds represented by the aforementioned formula (I) represents -Y-$(CH_2)_n$-B wherein B is a heterocyclic residue which has at least one nitrogen atom as the hetero atom, the compounds may exist as N-oxide compounds. The N-oxide compounds also fall within the scope of the present invention.

[0023] Specific examples of the compounds of the present invention are shown in Table 1 below. In the table, Me represents methyl group, Et represents ethyl group, and n-Pr represents normal propyl group.

Table 1

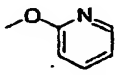
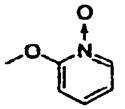
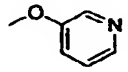
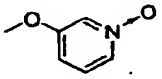
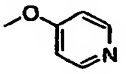
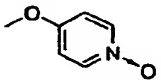
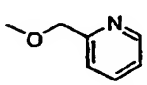
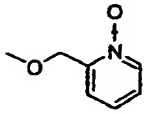
Compound No	X	R1	R2	R3	R4	R5
1	H	Me		H	H	H
2	H	Me		H	H	OMe
3	H	Me		H	H	F
4	H	Me		H	H	Cl
5	H	Me		H	H	Br
6	H	Me		H	H	I
7	H	Me		H	H	
8	H	Me		H	H	
9	H	Me		H	H	
10	H	Me		H	H	
11	H	Me		H	H	
12	H	Me		H	H	
13	H	Me		H	H	
14	H	Me		H	H	

Table 1 (continued)

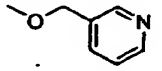
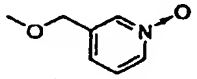
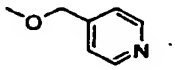
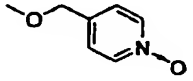
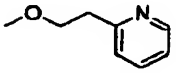
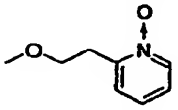
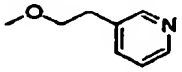
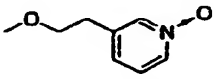
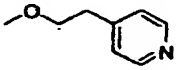
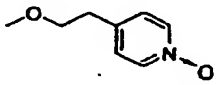
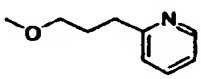
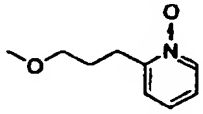
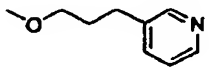
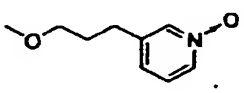
Compound No	X	R1	R2	R3	R4	R5
15	H	Me		H	H	
16	H	Me		H	H	
17	H	Me		H	H	
18	H	Me		H	H	
19	H	Me		H	H	
20	H	Me		H	H	
21	H	Me		H	H	
22	H	Me		H	H	
23	H	Me		H	H	
24	H	Me		H	H	
25	H	Me		H	H	
26	H	Me		H	H	
27	H	Me		H	H	
28	H	Me		H	H	

Table 1 (continued)

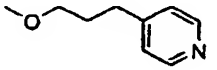
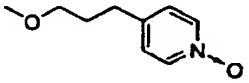
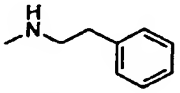
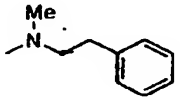
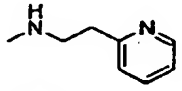
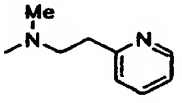
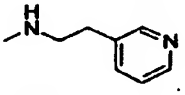
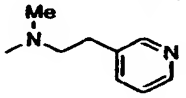
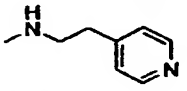
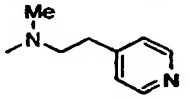
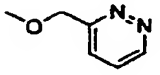
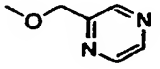
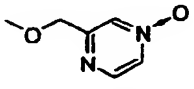
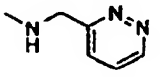
Compound No	X	R1	R2	R3	R4	R5
29	H	Me		H	H	
30	H	Me		H	H	
31	H	Me		H	H	
32	H	Me		H	H	
33	H	Me		H	H	
34	H	Me		H	H	
35	H	Me		H	H	
36	H	Me		H	H	
37	H	Me		H	H	
38	H	Me		H	H	
39	H	Me		H	H	
40	H	Me		H	H	
41	H	Me		H	H	
42	H	Me		H	H	

Table 1 (continued)

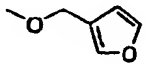
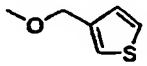
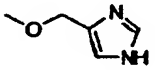
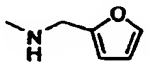
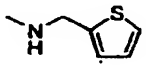
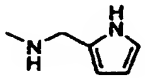
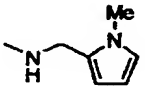
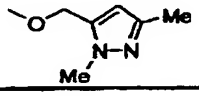
Compound No	X	R1	R2	R3	R4	R5
43	H	Me		H	H	
44	H	Me		H	H	
45	H	Me		H	H	
46	H	Me		H	H	
47	H	Me		H	H	
48	H	Me		H	H	
49	H	Me		H	H	
50	H	Me		H	H	
51	H	Me		H	Me	H
52	H	Me		H	Me	OMe
53	H	Me		H	Me	F
54	H	Me		H	Me	Cl
55	H	Me		H	Me	Br
56	H	Me		H	Me	I

Table 1 (continued)

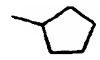
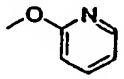
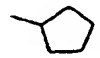
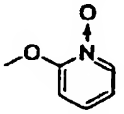
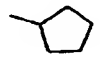
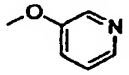
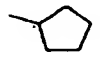
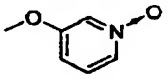
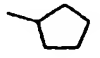
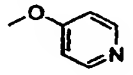
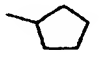
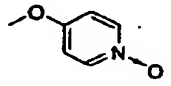
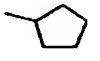
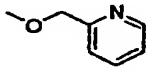
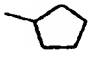
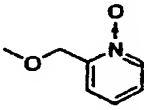
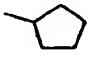
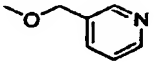
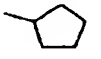
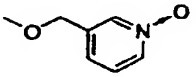
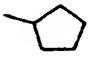
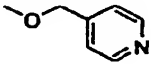
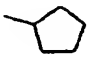
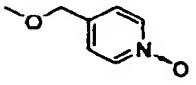
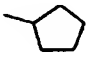
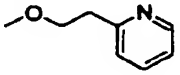
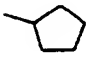
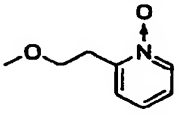
Compound No	X	R1	R2	R3	R4	R5
57	H	Me		H	Me	
58	H	Me		H	Me	
59	H	Me		H	Me	
60	H	Me		H	Me	
61	H	Me		H	Me	
62	H	Me		H	Me	
63	H	Me		H	Me	
64	H	Me		H	Me	
65	H	Me		H	Me	
66	H	Me		H	Me	
67	H	Me		H	Me	
68	H	Me		H	Me	
69	H	Me		H	Me	
70	H	Me		H	Me	

Table 1 (continued)

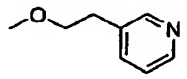
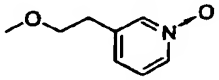
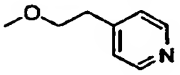
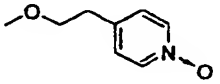
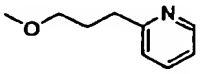
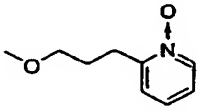
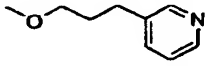
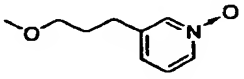
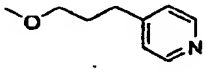
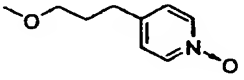
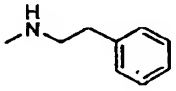
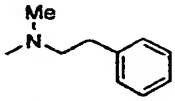
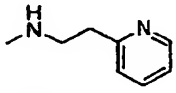
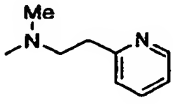
Compound No	X	R1	R2	R3	R4	R5
71	H	Me		H	Me	
72	H	Me		H	Me	
73	H	Me		H	Me	
74	H	Me		H	Me	
75	H	Me		H	Me	
76	H	Me		H	Me	
77	H	Me		H	Me	
78	H	Me		H	Me	
79	H	Me		H	Me	
80	H	Me		H	Me	
81	H	Me		H	Me	
82	H	Me		H	Me	
83	H	Me		H	Me	
84	H	Me		H	Me	

Table 1 (continued)

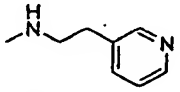
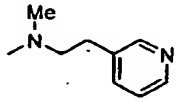
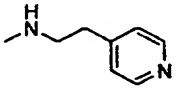
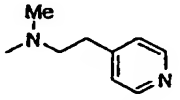
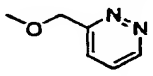
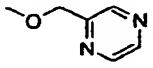
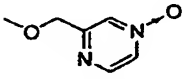
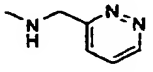
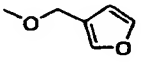
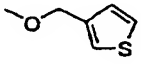
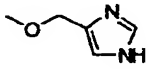
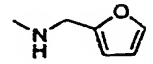
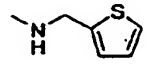
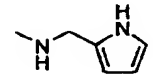
Compound No	X	R1	R2	R3	R4	R5
85	H	Me		H	Me	
86	H	Me		H	Me	
87	H	Me		H	Me	
88	H	Me		H	Me	
89	H	Me		H	Me	
90	H	Me		H	Me	
91	H	Me		H	Me	
92	H	Me		H	Me	
93	H	Me		H	Me	
94	H	Me		H	Me	
95	H	Me		H	Me	
96	H	Me		H	Me	
97	H	Me		H	Me	
98	H	Me		H	Me	

Table 1 (continued)

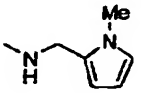
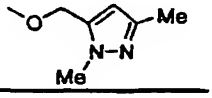
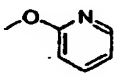
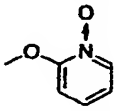
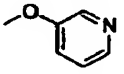
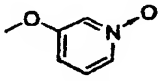
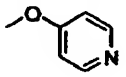
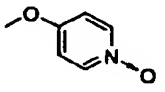
Compound No	X	R1	R2	R3	R4	R5
99	H	Me		H	Me	
100	H	Me		H	Me	
101	H	Me		H	Et	H
102	H	Me		H	Et	OMe
103	H	Me		H	Et	F
104	H	Me		H	Et	Cl
105	H	Me		H	Et	Br
106	H	Me		H	Et	I
107	H	Me		H	Et	
108	H	Me		H	Et	
109	H	Me		H	Et	
110	H	Me		H	Et	
111	H	Me		H	Et	
112	H	Me		H	Et	

Table 1 (continued)

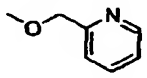
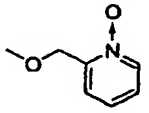
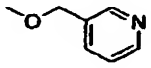
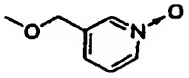
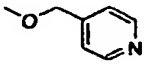
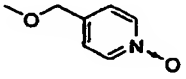
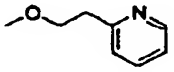
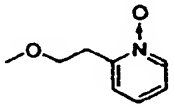
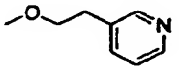
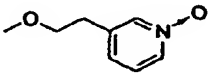
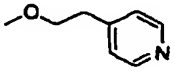
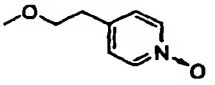
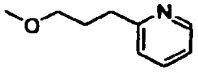
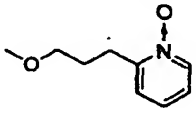
Compound No	X	R1	R2	R3	R4	R5
113	H	Me		H	Et	
114	H	Me		H	Et	
115	H	Me		H	Et	
116	H	Me		H	Et	
117	H	Me		H	Et	
118	H	Me		H	Et	
119	H	Me		H	Et	
120	H	Me		H	Et	
121	H	Me		H	Et	
122	H	Me		H	Et	
123	H	Me		H	Et	
124	H	Me		H	Et	
125	H	Me		H	Et	
126	H	Me		H	Et	

Table 1 (continued)

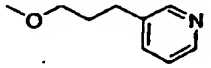
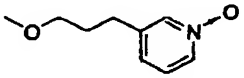
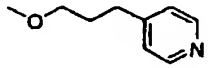
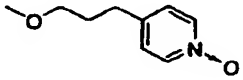
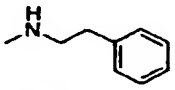
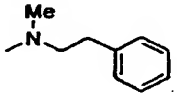
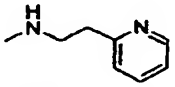
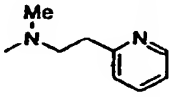
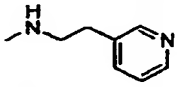
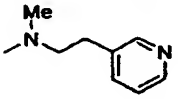
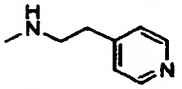
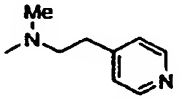
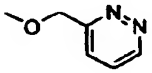
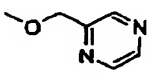
Compound No	X	R1	R2	R3	R4	R5
127	H	Me		H	Et	
128	H	Me		H	Et	
129	H	Me		H	Et	
130	H	Me		H	Et	
131	H	Me		H	Et	
132	H	Me		H	Et	
133	H	Me		H	Et	
134	H	Me		H	Et	
135	H	Me		H	Et	
136	H	Me		H	Et	
137	H	Me		H	Et	
138	H	Me		H	Et	
139	H	Me		H	Et	
140	H	Me		H	Et	

Table 1 (continued)

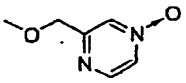
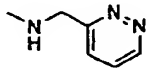
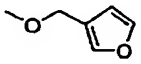
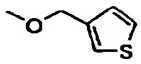
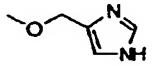
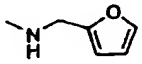
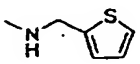
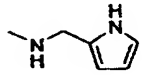
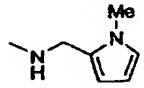
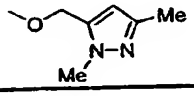
Compound No	X	R1	R2	R3	R4	R5
141	H	Me		H	Et	
142	H	Me		H	Et	
143	H	Me		H	Et	
144	H	Me		H	Et	
145	H	Me		H	Et	
146	H	Me		H	Et	
147	H	Me		H	Et	
148	H	Me		H	Et	
149	H	Me		H	Et	
150	H	Me		H	Et	
151	H	Me		H	OMe	H
152	H	Me		H	OMe	OMe
153	H	Me		H	OMe	F
154	H	Me		H	OMe	Cl

Table 1 (continued)

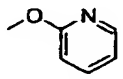
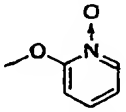
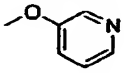
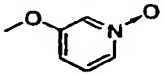
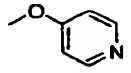
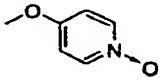
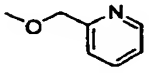
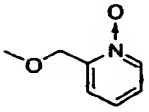
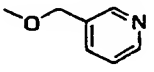
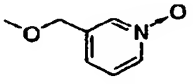
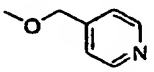
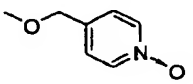
Compound No	X	R1	R2	R3	R4	R5
155	H	Me		H	OMe	Br
156	H	Me		H	OMe	I
157	H	Me		H	OMe	
158	H	Me		H	OMe	
159	H	Me		H	OMe	
160	H	Me		H	OMe	
161	H	Me		H	OMe	
162	H	Me		H	OMe	
163	H	Me		H	OMe	
164	H	Me		H	OMe	
165	H	Me		H	OMe	
166	H	Me		H	OMe	
167	H	Me		H	OMe	
168	H	Me		H	OMe	

Table 1 (continued)

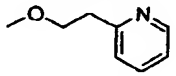
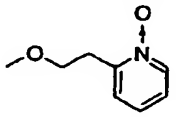
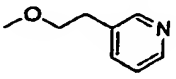
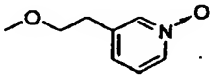
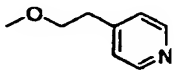
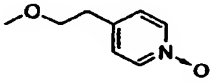
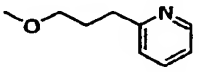
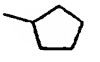
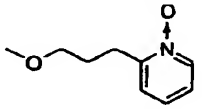
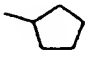
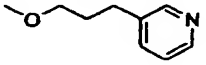
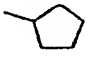
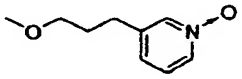
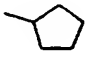
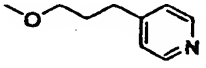
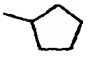
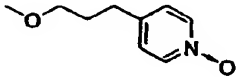
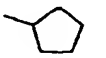
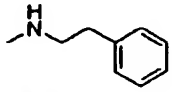
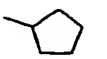
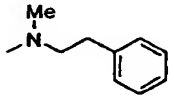
Compound No	X	R1	R2	R3	R4	R5
169	H	Me		H	OMe	
170	H	Me		H	OMe	
171	H	Me		H	OMe	
172	H	Me		H	OMe	
173	H	Me		H	OMe	
174	H	Me		H	OMe	
175	H	Me		H	OMe	
176	H	Me		H	OMe	
177	H	Me		H	OMe	
178	H	Me		H	OMe	
179	H	Me		H	OMe	
180	H	Me		H	OMe	
181	H	Me		H	OMe	
182	H	Me		H	OMe	

Table 1 (continued)

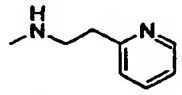
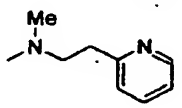
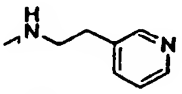
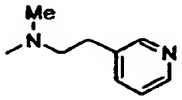
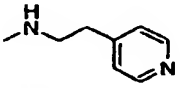
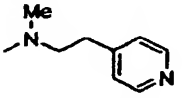
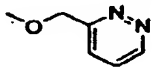
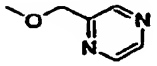
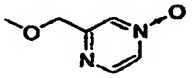
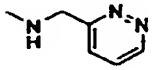
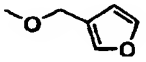
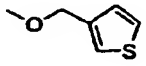
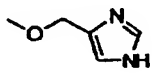
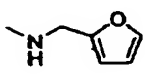
Compound No	X	R1	R2	R3	R4	R5
183	H	Me		H	OMe	
184	H	Me		H	OMe	
185	H	Me		H	OMe	
186	H	Me		H	OMe	
187	H	Me		H	OMe	
188	H	Me		H	OMe	
189	H	Me		H	OMe	
190	H	Me		H	OMe	
191	H	Me		H	OMe	
192	H	Me		H	OMe	
193	H	Me		H	OMe	
194	H	Me		H	OMe	
195	H	Me		H	OMe	
196	H	Me		H	OMe	

Table 1 (continued)

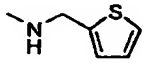
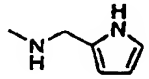
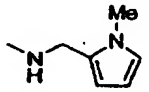
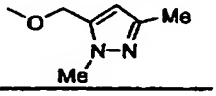
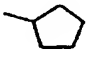
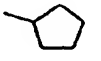
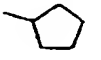
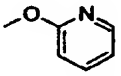
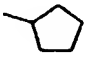
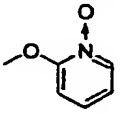
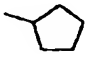
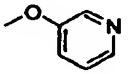
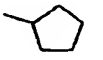
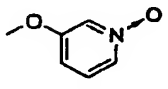
Compound No	X	R1	R2	R3	R4	R5
197	H	Me		H	OMe	
198	H	Me		H	OMe	
199	H	Me		H	OMe	
200	H	Me		H	OMe	
201	H	Me		H	NH_2	H
202	H	Me		H	NH_2	OMe
203	H	Me		H	NH_2	F
204	H	Me		H	NH_2	Cl
205	H	Me		H	NH_2	Br
206	H	Me		H	NH_2	I
207	H	Me		H	NH_2	
208	H	Me		H	NH_2	
209	H	Me		H	NH_2	
210	H	Me		H	NH_2	

Table 1 (continued)

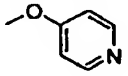
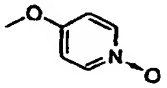
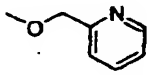
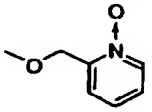
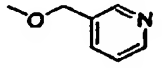
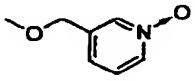
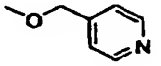
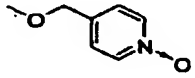
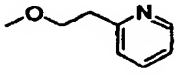
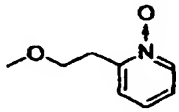
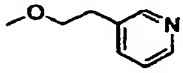
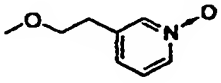
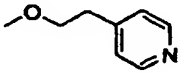
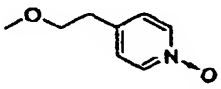
Compound No	X	R1	R2	R3	R4	R5
211	H	Me		H	NH_2	
212	H	Me		H	NH_2	
213	H	Me		H	NH_2	
214	H	Me		H	NH_2	
215	H	Me		H	NH_2	
216	H	Me		H	NH_2	
217	H	Me		H	NH_2	
218	H	Me		H	NH_2	
219	H	Me		H	NH_2	
220	H	Me		H	NH_2	
221	H	Me		H	NH_2	
222	H	Me		H	NH_2	
223	H	Me		H	NH_2	
224	H	Me		H	NH_2	

Table 1 (continued)

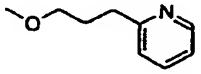
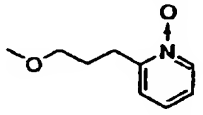
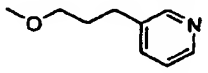
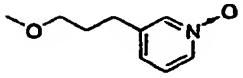
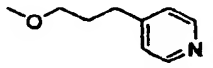
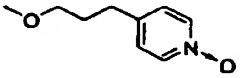
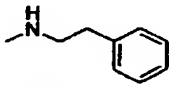
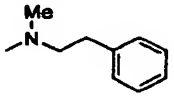
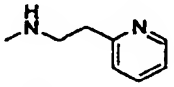
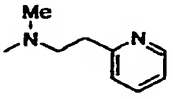
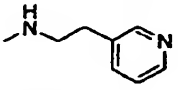
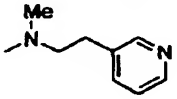
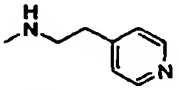
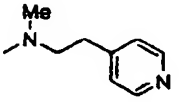
Compound No	X	R1	R2	R3	R4	R5
225	H	Me		H	NH_2	
226	H	Me		H	NH_2	
227	H	Me		H	NH_2	
228	H	Me		H	NH_2	
229	H	Me		H	NH_2	
230	H	Me		H	NH_2	
231	H	Me		H	NH_2	
232	H	Me		H	NH_2	
233	H	Me		H	NH_2	
234	H	Me		H	NH_2	
235	H	Me		H	NH_2	
236	H	Me		H	NH_2	
237	H	Me		H	NH_2	
238	H	Me		H	NH_2	

Table 1 (continued)

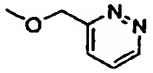
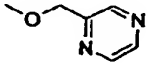
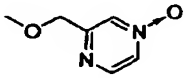
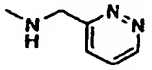
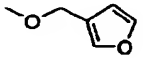
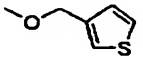
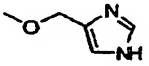
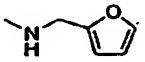
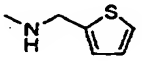
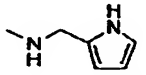
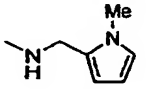
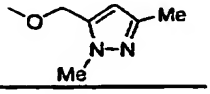
Compound No	X	R1	R2	R3	R4	R5
239	H	Me		H	NH_2	
240	H	Me		H	NH_2	
241	H	Me		H	NH_2	
242	H	Me		H	NH_2	
243	H	Me		H	NH_2	
244	H	Me		H	NH_2	
245	H	Me		H	NH_2	
246	H	Me		H	NH_2	
247	H	Me		H	NH_2	
248	H	Me		H	NH_2	
249	H	Me		H	NH_2	
250	H	Me		H	NH_2	
251	H	Me		H	NHMe	H
252	H	Me		H	NHMe	OMe

Table 1 (continued)

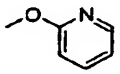
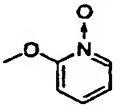
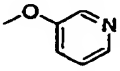
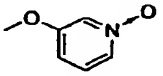
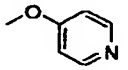
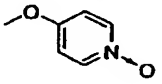
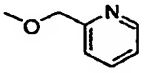
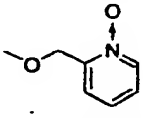
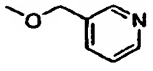
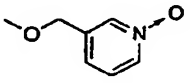
Compound No	X	R1	R2	R3	R4	R5
253	H	Me		H	NHMe	F
254	H	Me		H	NHMe	Cl
255	H	Me		H	NHMe	Br
256	H	Me		H	NHMe	I
257	H	Me		H	NHMe	
258	H	Me		H	NHMe	
259	H	Me		H	NHMe	
260	H	Me		H	NHMe	
261	H	Me		H	NHMe	
262	H	Me		H	NHMe	
263	H	Me		H	NHMe	
264	H	Me		H	NHMe	
265	H	Me		H	NHMe	
266	H	Me		H	NHMe	

Table 1 (continued)

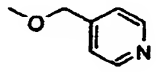
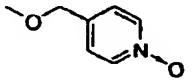
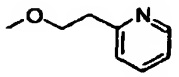
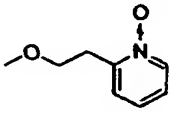
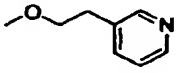
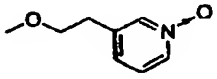
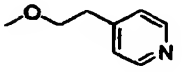
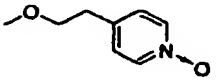
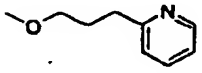
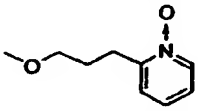
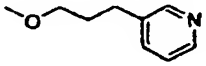
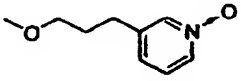
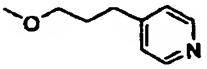
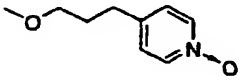
Compound No	X	R1	R2	R3	R4	R5
267	H	Me		H	NHMe	
268	H	Me		H	NHMe	
269	H	Me		H	NHMe	
270	H	Me		H	NHMe	
271	H	Me		H	NHMe	
272	H	Me		H	NHMe	
273	H	Me		H	NHMe	
274	H	Me		H	NHMe	
275	H	Me		H	NHMe	
276	H	Me		H	NHMe	
277	H	Me		H	NHMe	
278	H	Me		H	NHMe	
279	H	Me		H	NHMe	
280	H	Me		H	NHMe	

Table 1 (continued)

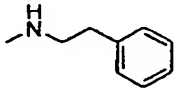
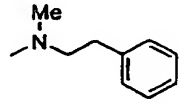
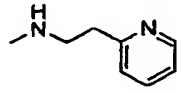
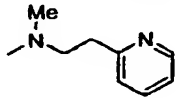
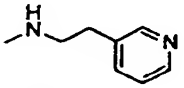
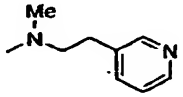
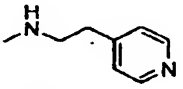
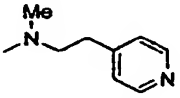
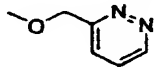
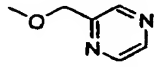
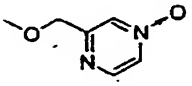
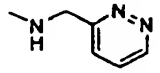
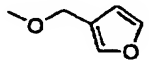
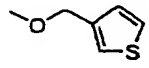
Compound No	X	R1	R2	R3	R4	R5
281	H	Me		H	NHMe	
282	H	Me		H	NHMe	
283	H	Me		H	NHMe	
284	H	Me		H	NHMe	
285	H	Me		H	NHMe	
286	H	Me		H	NHMe	
287	H	Me		H	NHMe	
288	H	Me		H	NHMe	
289	H	Me		H	NHMe	
290	H	Me		H	NHMe	
291	H	Me		H	NHMe	
292	H	Me		H	NHMe	
293	H	Me		H	NHMe	
294	H	Me		H	NHMe	

Table 1 (continued)

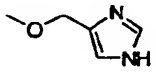
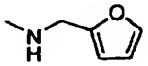
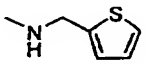
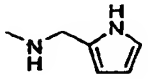
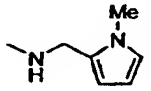
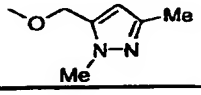
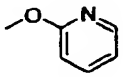
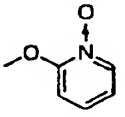
Compound No	X	R1	R2	R3	R4	R5
295	H	Me		H	NHMe	
296	H	Me		H	NHMe	
297	H	Me		H	NHMe	
298	H	Me		H	NHMe	
299	H	Me		H	NHMe	
300	H	Me		H	NHMe	
301	H	Me		H	NHEt	H
302	H	Me		H	NHEt	OMe
303	H	Me		H	NHEt	F
304	H	Me		H	NHEt	Cl
305	H	Me		H	NHEt	Br
306	H	Me		H	NHEt	I
307	H	Me		H	NHEt	
308	H	Me		H	NHEt	

Table 1 (continued)

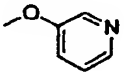
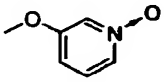
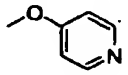
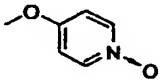
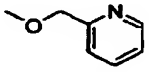
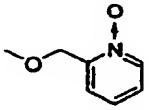
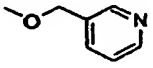
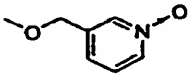
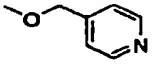
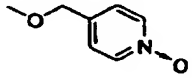
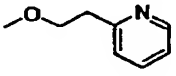
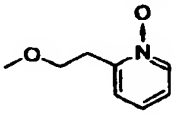
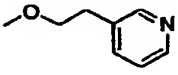
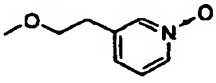
Compound No	X	R1	R2	R3	R4	R5
309	H	Me		H	NHEt	
310	H	Me		H	NHEt	
311	H	Me		H	NHEt	
312	H	Me		H	NHEt	
313	H	Me		H	NHEt	
314	H	Me		H	NHEt	
315	H	Me		H	NHEt	
316	H	Me		H	NHEt	
317	H	Me		H	NHEt	
318	H	Me		H	NHEt	
319	H	Me		H	NHEt	
320	H	Me		H	NHEt	
321	H	Me		H	NHEt	
322	H	Me		H	NHEt	

Table 1 (continued)

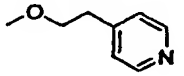
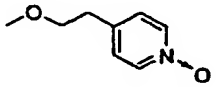
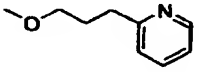
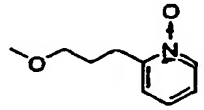
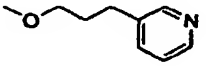
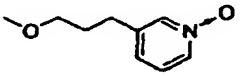
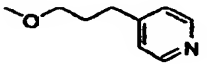
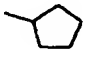
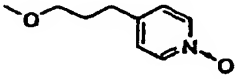
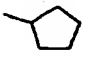
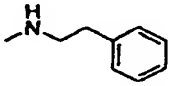
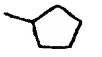
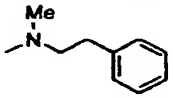
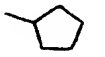
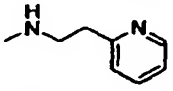
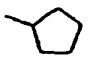
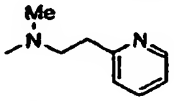
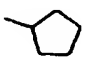
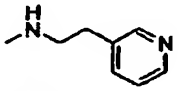
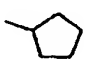
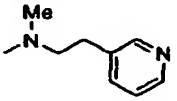
Compound No	X	R1	R2	R3	R4	R5
323	H	Me		H	NHEt	
324	H	Me		H	NHEt	
325	H	Me		H	NHEt	
326	H	Me		H	NHEt	
327	H	Me		H	NHEt	
328	H	Me		H	NHEt	
329	H	Me		H	NHEt	
330	H	Me		H	NHEt	
331	H	Me		H	NHEt	
332	H	Me		H	NHEt	
333	H	Me		H	NHEt	
334	H	Me		H	NHEt	
335	H	Me		H	NHEt	
336	H	Me		H	NHEt	

Table 1 (continued)

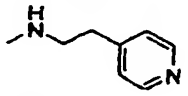
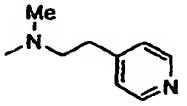
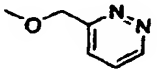
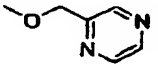
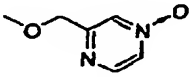
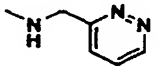
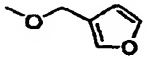
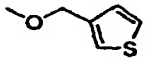
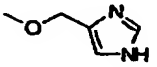
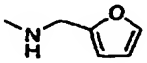
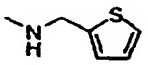
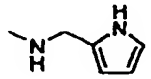
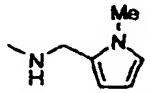
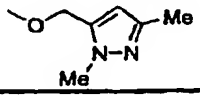
Compound No	X	R1	R2	R3	R4	R5
337	H	Me		H	NHEt	
338	H	Me		H	NHEt	
339	H	Me		H	NHEt	
340	H	Me		H	NHEt	
341	H	Me		H	NHEt	
342	H	Me		H	NHEt	
343	H	Me		H	NHEt	
344	H	Me		H	NHEt	
345	H	Me		H	NHEt	
346	H	Me		H	NHEt	
347	H	Me		H	NHEt	
348	H	Me		H	NHEt	
349	H	Me		H	NHEt	
350	H	Me		H	NHEt	

Table 1 (continued)

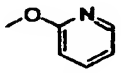
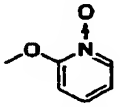
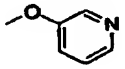
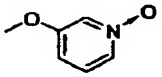
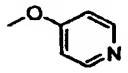
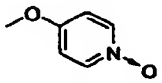
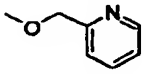
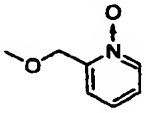
Compound No	X	R1	R2	R3	R4	R5
351	H	Me		H	NH*n*-Pr	H
352	H	Me		H	NH*n*-Pr	OMe
353	H	Me		H	NH*n*-Pr	F
354	H	Me		H	NH*n*-Pr	Cl
355	H	Me		H	NH*n*-Pr	Br
356	H	Me		H	NH*n*-Pr	I
357	H	Me		H	NH*n*-Pr	
358	H	Me		H	NH*n*-Pr	
359	H	Me		H	NH*n*-Pr	
360	H	Me		H	NH*n*-Pr	
361	H	Me		H	NH*n*-Pr	
362	H	Me		H	NH*n*-Pr	
363	H	Me		H	NH*n*-Pr	
364	H	Me		H	NH*n*-Pr	

Table 1 (continued)

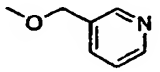
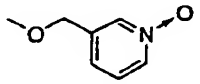
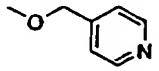
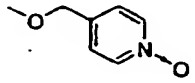
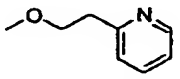
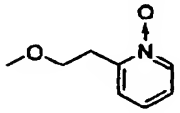
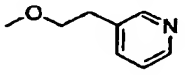
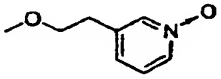
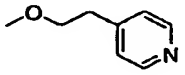
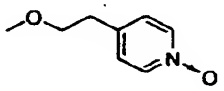
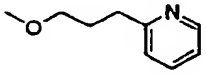
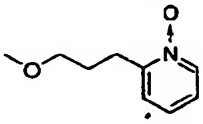
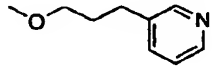
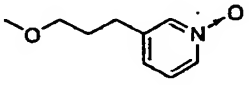
Compound No	X	R1	R2	R3	R4	R5
365	H	Me		H	NH*n*-Pr	
366	H	Me		H	NH*n*-Pr	
367	H	Me		H	NH*n*-Pr	
368	H	Me		H	NH*n*-Pr	
369	H	Me		H	NH*n*-Pr	
370	H	Me		H	NH*n*-Pr	
371	H	Me		H	NH*n*-Pr	
372	H	Me		H	NH*n*-Pr	
373	H	Me		H	NH*n*-Pr	
374	H	Me		H	NH*n*-Pr	
375	H	Me		H	NH*n*-Pr	
376	H	Me		H	NH*n*-Pr	
377	H	Me		H	NH*n*-Pr	
378	H	Me		H	NH*n*-Pr	

Table 1 (continued)

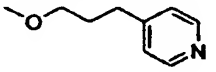
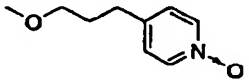
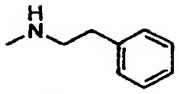
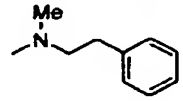
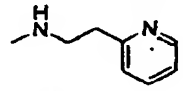
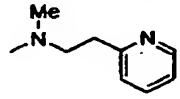
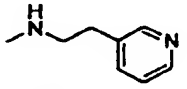
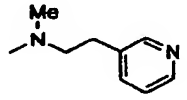
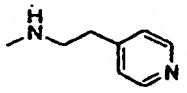
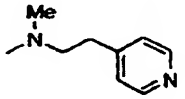
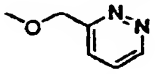
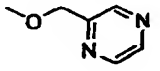
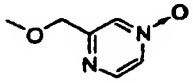
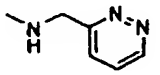
Compound No	X	R1	R2	R3	R4	R5
379	H	Me		H	NH*n*-Pr	
380	H	Me		H	NH*n*-Pr	
381	H	Me		H	NH*n*-Pr	
382	H	Me		H	NH*n*-Pr	
383	H	Me		H	NH*n*-Pr	
384	H	Me		H	NH*n*-Pr	
385	H	Me		H	NH*n*-Pr	
386	H	Me		H	NH*n*-Pr	
387	H	Me		H	NH*n*-Pr	
388	H	Me		H	NH*n*-Pr	
389	H	Me		H	NH*n*-Pr	
390	H	Me		H	NH*n*-Pr	
391	H	Me		H	NH*n*-Pr	
392	H	Me		H	NH*n*-Pr	

Table 1 (continued)

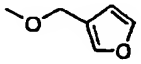
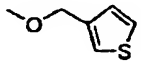
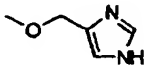
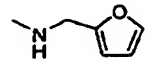
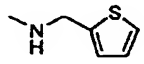
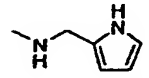
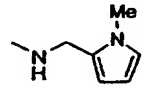
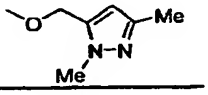
Compound No	X	R1	R2	R3	R4	R5
393	H	Me		H	NH*n*-Pr	
394	H	Me		H	NH*n*-Pr	
395	H	Me		H	NH*n*-Pr	
396	H	Me		H	NH*n*-Pr	
397	H	Me		H	NH*n*-Pr	
398	H	Me		H	NH*n*-Pr	
399	H	Me		H	NH*n*-Pr	
400	H	Me		H	NH*n*-Pr	
401	H	Me		H	NMe_2	H
402	H	Me		H	NMe_2	OMe
403	H	Me		H	NMe_2	F
404	H	Me		H	NMe_2	Cl
405	H	Me		H	NMe_2	Br
406	H	Me		H	NMe_2	I

Table 1 (continued)

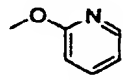
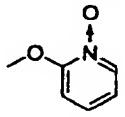
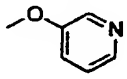
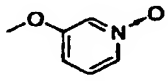
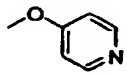
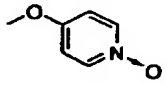
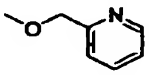
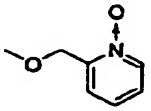
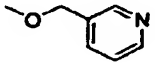
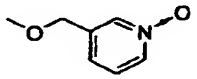
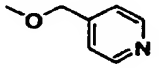
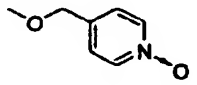
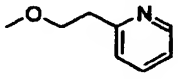
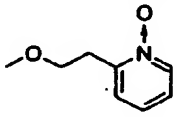
Compound No	X	R1	R2	R3	R4	R5
407	H	Me		H	NMe_2	
408	H	Me		H	NMe_2	
409	H	Me		H	NMe_2	
410	H	Me		H	NMe_2	
411	H	Me		H	NMe_2	
412	H	Me		H	NMe_2	
413	H	Me		H	NMe_2	
414	H	Me		H	NMe_2	
415	H	Me		H	NMe_2	
416	H	Me		H	NMe_2	
417	H	Me		H	NMe_2	
418	H	Me		H	NMe_2	
419	H	Me		H	NMe_2	
420	H	Me		H	NMe_2	

Table 1 (continued)

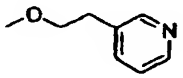
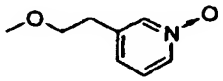
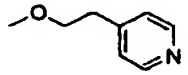
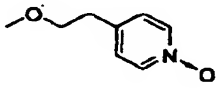
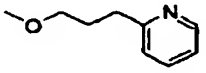
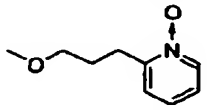
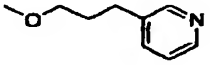
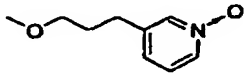
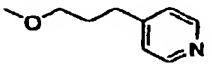
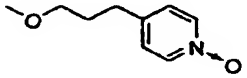
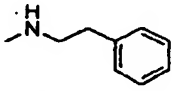
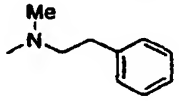
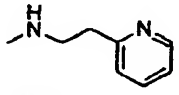
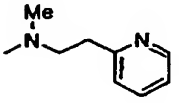
Compound No	X	R1	R2	R3	R4	R5
421	H	Me		H	NMe_2	
422	H	Me		H	NMe_2	
423	H	Me		H	NMe_2	
424	H	Me		H	NMe_2	
425	H	Me		H	NMe_2	
426	H	Me		H	NMe_2	
427	H	Me		H	NMe_2	
428	H	Me		H	NMe_2	
429	H	Me		H	NMe_2	
430	H	Me		H	NMe_2	
431	H	Me		H	NMe_2	
432	H	Me		H	NMe_2	
433	H	Me		H	NMe_2	
434	H	Me		H	NMe_2	

Table 1 (continued)

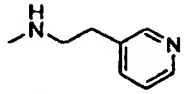
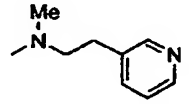
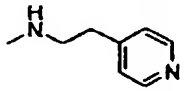
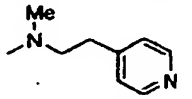
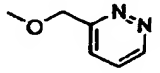
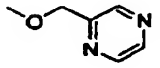
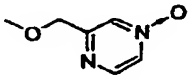
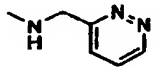
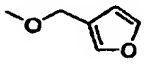
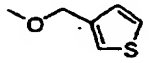
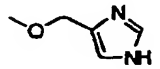
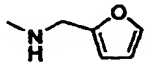
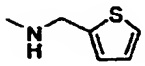
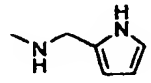
Compound No	X	R1	R2	R3	R4	R5
435	H	Me		H	NMe_2	
436	H	Me		H	NMe_2	
437	H	Me		H	NMe_2	
438	H	Me		H	NMe_2	
439	H	Me		H	NMe_2	
440	H	Me		H	NMe_2	
441	H	Me		H	NMe_2	
442	H	Me		H	NMe_2	
443	H	Me		H	NMe_2	
444	H	Me		H	NMe_2	
445	H	Me		H	NMe_2	
446	H	Me		H	NMe_2	
447	H	Me		H	NMe_2	
448	H	Me		H	NMe_2	

Table 1 (continued)

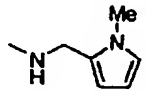
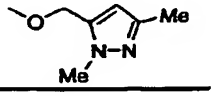
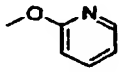
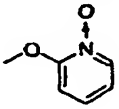
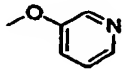
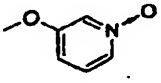
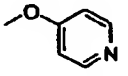
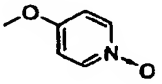
Compound No	X	R1	R2	R3	R4	R5
449	H	Me		H	NMe_2	
450	H	Me		H	NMe_2	
451	H	Me		H	Cl	H
452	H	Me		H	Cl	OMe
453	H	Me		H	Cl	F
454	H	Me		H	Cl	Cl
455	H	Me		H	Cl	Br
456	H	Me		H	Cl	I
457	H	Me		H	Cl	
458	H	Me		H	Cl	
459	H	Me		H	Cl	
460	H	Me		H	Cl	
461	H	Me		H	Cl	
462	H	Me		H	Cl	

Table 1 (continued)

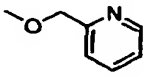
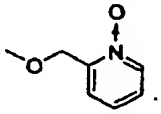
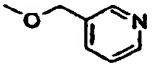
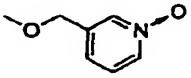
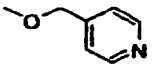
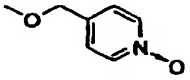
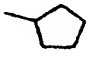
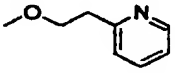
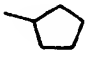
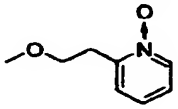
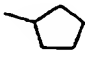
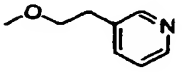
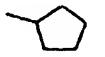
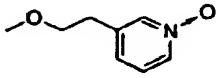
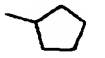
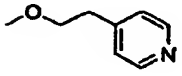
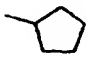
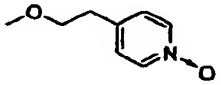
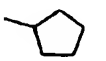
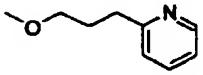
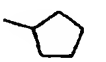
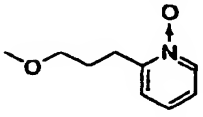
Compound No	X	R1	R2	R3	R4	R5
463	H	Me		H	Cl	
464	H	Me		H	Cl	
465	H	Me		H	Cl	
466	H	Me		H	Cl	
467	H	Me		H	Cl	
468	H	Me		H	Cl	
469	H	Me		H	Cl	
470	H	Me		H	Cl	
471	H	Me		H	Cl	
472	H	Me		H	Cl	
473	H	Me		H	Cl	
474	H	Me		H	Cl	
475	H	Me		H	Cl	
476	H	Me		H	Cl	

Table 1 (continued)

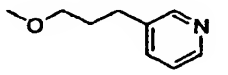
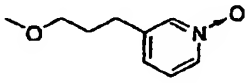
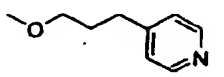
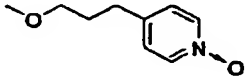
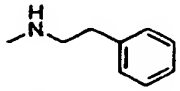
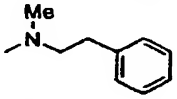
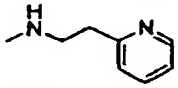
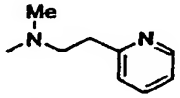
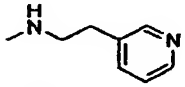
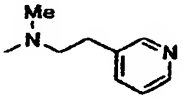
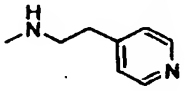
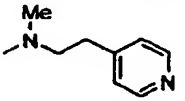
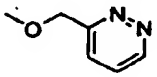
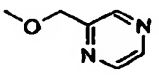
Compound No	X	R1	R2	R3	R4	R5
477	H	Me		H	Cl	
478	H	Me		H	Cl	
479	H	Me		H	Cl	
480	H	Me		H	Cl	
481	H	Me		H	Cl	
482	H	Me		H	Cl	
483	H	Me		H	Cl	
484	H	Me		H	Cl	
485	H	Me		H	Cl	
486	H	Me		H	Cl	
487	H	Me		H	Cl	
488	H	Me		H	Cl	
489	H	Me		H	Cl	
490	H	Me		H	Cl	

Table 1 (continued)

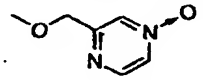
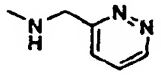
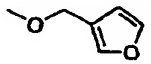
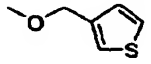
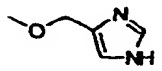
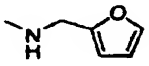
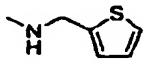
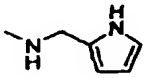
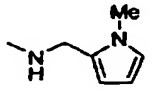
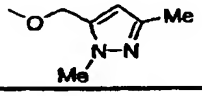
Compound No	X	R1	R2	R3	R4	R5
491	H	Me		H	Cl	
492	H	Me		H	Cl	
493	H	Me		H	Cl	
494	H	Me		H	Cl	
495	H	Me		H	Cl	
496	H	Me		H	Cl	
497	H	Me		H	Cl	
498	H	Me		H	Cl	
499	H	Me		H	Cl	
500	H	Me		H	Cl	
501	H	Me		H		H
502	H	Me		H		OMe
503	H	Me		H		F
504	H	Me		H		Cl

Table 1 (continued)

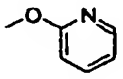
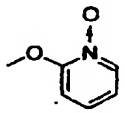
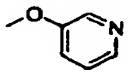
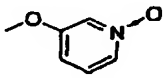
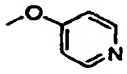
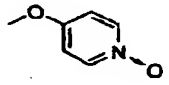
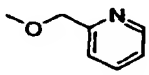
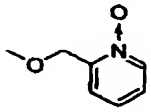
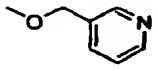
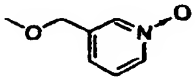
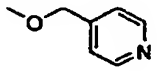
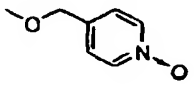
Compound No	X	R1	R2	R3	R4	R5
505	H	Me		H		Br
506	H	Me		H		I
507	H	Me		H		
508	H	Me		H		
509	H	Me		H		
510	H	Me		H		
511	H	Me		H		
512	H	Me		H		
513	H	Me		H		
514	H	Me		H		
515	H	Me		H		
516	H	Me		H		
517	H	Me		H		
518	H	Me		H		

Table 1 (continued)

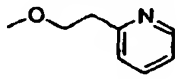
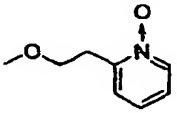
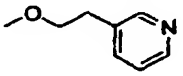
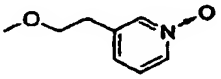
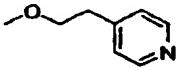
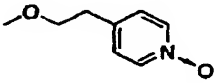
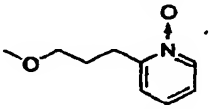
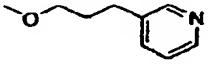
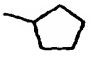
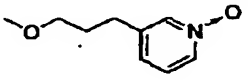
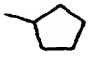
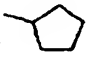
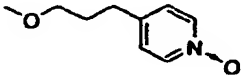
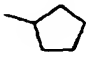
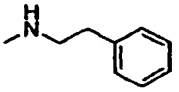
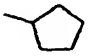
Compound No	X	R1	R2	R3	R4	R5
519	H	Me		H		
520	H	Me		H		
521	H	Me		H		
522	H	Me		H		
523	H	Me		H		
524	H	Me		H		
525	H	Me		H		
526	H	Me		H		
527	H	Me		H		
528	H	Me		H		
529	H	Me		H		
530	H	Me		H		
531	H	Me		H		
532	H	Me		H		

Table 1 (continued)

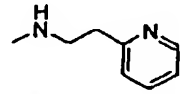
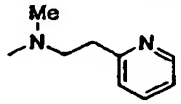
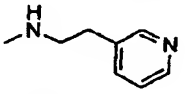
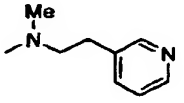
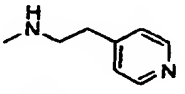
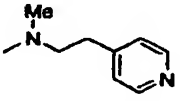
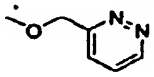
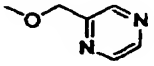
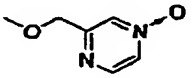
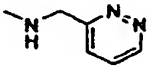
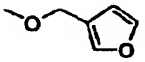
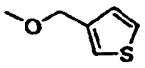
Compound No	X	R1	R2	R3	R4	R5
533	H	Me		H		
534	H	Me		H		
535	H	Me		H		
536	H	Me		H		
537	H	Me		H		
538	H	Me		H		
539	H	Me		H		
540	H	Me		H		
541	H	Me		H		
542	H	Me		H		
543	H	Me		H		
544	H	Me		H		
545	H	Me		H		
546	H	Me		H		

Table 1 (continued)

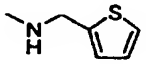
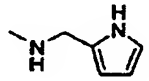
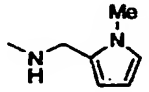
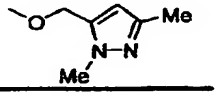
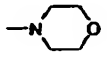
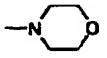
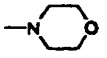
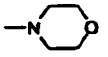
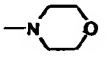
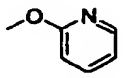
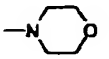
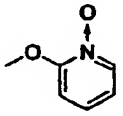
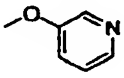
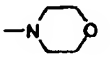
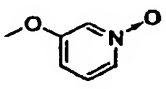
Compound No	X	R1	R2	R3	R4	R5
547	H	Me		H		
548	H	Me		H		
549	H	Me		H		
550	H	Me		H		
551	H	Me		H		H
552	H	Me		H		OMe
553	H	Me		H		F
554	H	Me		H		Cl
555	H	Me		H		Br
556	H	Me		H		I
557	H	Me		H		
558	H	Me		H		
559	H	Me		H		
560	H	Me		H		

Table 1 (continued)

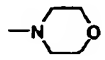
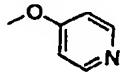
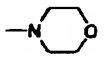
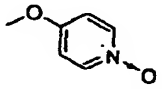
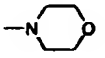
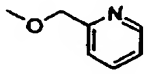
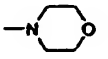
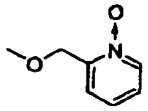
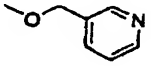
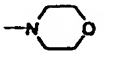
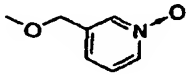
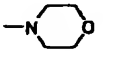
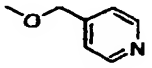
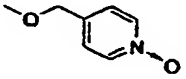
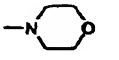
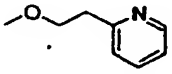
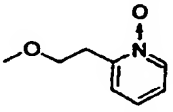
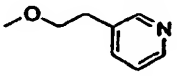
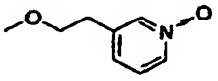
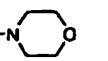
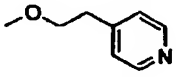
Compound No	X	R1	R2	R3	R4	R5
561	H	Me		H		
562	H	Me		H		
563	H	Me		H		
564	H	Me		H		
565	H	Me		H		
566	H	Me		H		
567	H	Me		H		
568	H	Me		H		
569	H	Me		H		
570	H	Me		H		
571	H	Me		H		
572	H	Me		H		
573	H	Me		H		
574	H	Me		H		

Table 1 (continued)

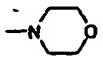
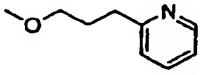
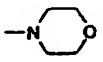
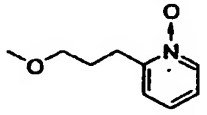
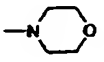
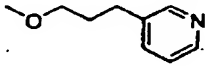
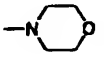
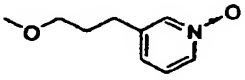
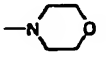
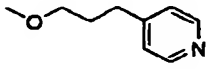
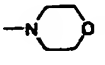
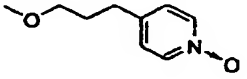
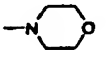
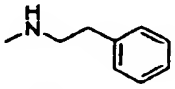
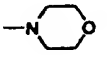
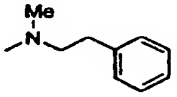
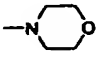
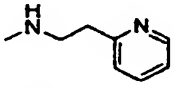
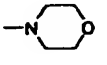
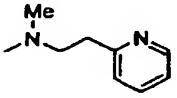
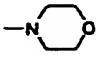
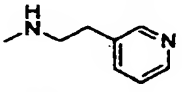
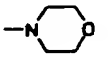
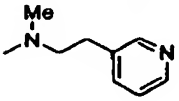
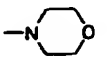
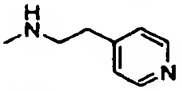
Compound No	X	R1	R2	R3	R4	R5
575	H	Me		H		
576	H	Me		H		
577	H	Me		H		
578	H	Me		H		
579	H	Me		H		
580	H	Me		H		
581	H	Me		H		
582	H	Me		H		
583	H	Me		H		
584	H	Me		H		
585	H	Me		H		
586	H	Me		H		
587	H	Me		H		
588	H	Me		H		

Table 1 (continued)

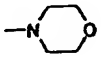
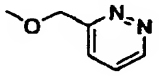
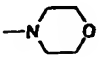
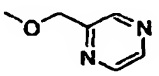
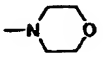
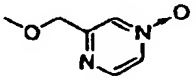
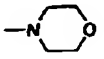
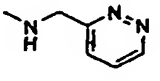
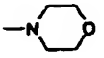
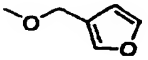
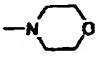
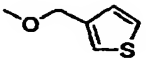
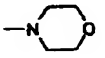
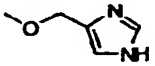
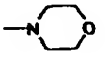
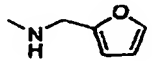
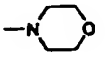
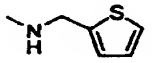
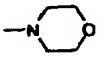
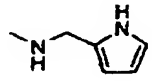
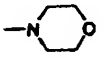
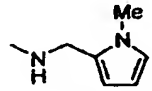
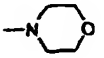
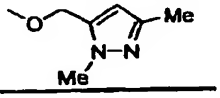
Compound No	X	R1	R2	R3	R4	R5
589	H	Me		H		
590	H	Me		H		
591	H	Me		H		
592	H	Me		H		
593	H	Me		H		
594	H	Me		H		
595	H	Me		H		
596	H	Me		H		
597	H	Me		H		
598	H	Me		H		
599	H	Me		H		
600	H	Me		H		
601	H	Me		Me	H	H
602	H	Me		Me	H	OMe

Table 1 (continued)

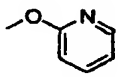
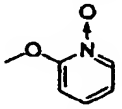
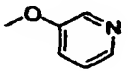
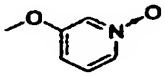
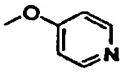
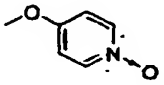
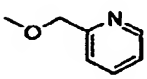
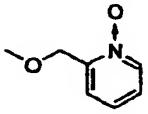
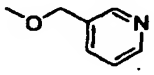
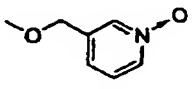
Compound No	X	R1	R2	R3	R4	R5
603	H	Me		Me	H	F
604	H	Me		Me	H	Cl
605	H	Me		Me	H	Br
606	H	Me		Me	H	I
607	H	Me		Me	H	
608	H	Me		Me	H	
609	H	Me		Me	H	
610	H	Me		Me	H	
611	H	Me		Me	H	
612	H	Me		Me	H	
613	H	Me		Me	H	
614	H	Me		Me	H	
615	H	Me		Me	H	
616	H	Me		Me	H	

Table 1 (continued)

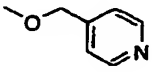
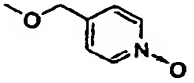
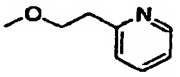
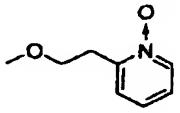
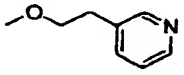
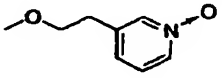
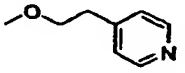
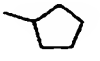
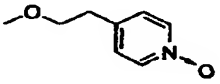
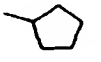
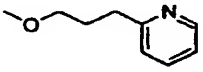
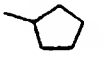
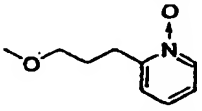
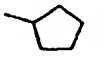
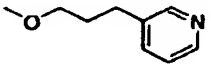
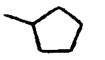
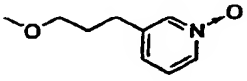
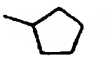
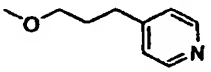
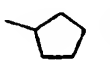
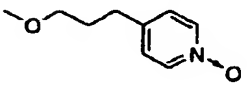
Compound No	X	R1	R2	R3	R4	R5
617	H	Me		Me	H	
618	H	Me		Me	H	
619	H	Me		Me	H	
620	H	Me		Me	H	
621	H	Me		Me	H	
622	H	Me		Me	H	
623	H	Me		Me	H	
624	H	Me		Me	H	
625	H	Me		Me	H	
626	H	Me		Me	H	
627	H	Me		Me	H	
628	H	Me		Me	H	
629	H	Me		Me	H	
630	H	Me		Me	H	

Table 1 (continued)

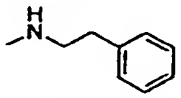
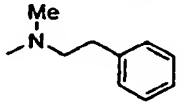
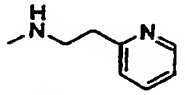
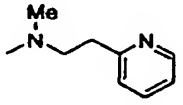
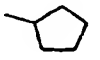
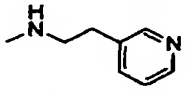
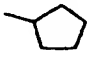
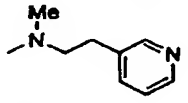
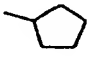
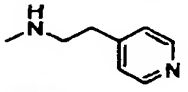
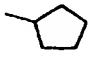
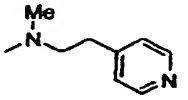
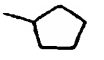
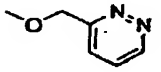
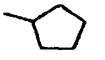
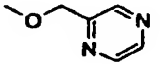
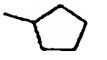
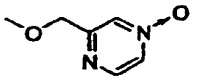
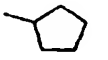
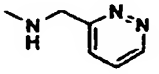
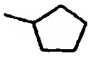
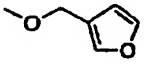
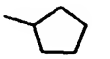
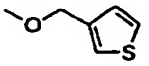
Compound No	X	R1	R2	R3	R4	R5
631	H	Me		Me	H	
632	H	Me		Me	H	
633	H	Me		Me	H	
634	H	Me		Me	H	
635	H	Me		Me	H	
636	H	Me		Me	H	
637	H	Me		Me	H	
638	H	Me		Me	H	
639	H	Me		Me	H	
640	H	Me		Me	H	
641	H	Me		Me	H	
642	H	Me		Me	H	
643	H	Me		Me	H	
644	H	Me		Me	H	

Table 1 (continued)

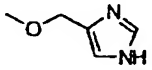
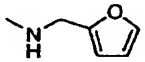
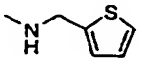
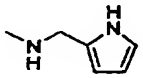
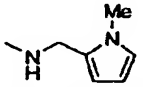
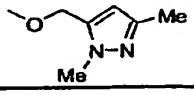
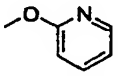
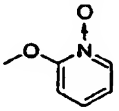
Compound No	X	R1	R2	R3	R4	R5
645	H	Me		Me	H	
646	H	Me		Me	H	
647	H	Me		Me	H	
648	H	Me		Me	H	
649	H	Me		Me	H	
650	H	Me		Me	H	
651	H	Me		Me	Me	H
652	H	Me		Me	Me	OMe
653	H	Me		Me	Me	F
654	H	Me		Me	Me	Cl
655	H	Me		Me	Me	Br
656	H	Me		Me	Me	I
657	H	Me		Me	Me	
658	H	Me		Me	Me	

Table 1 (continued)

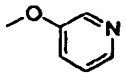
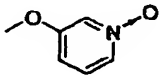
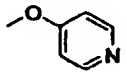
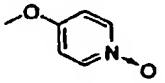
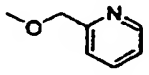
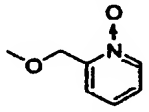
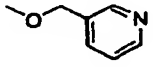
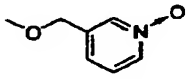
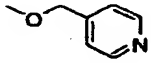
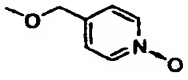
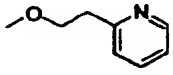
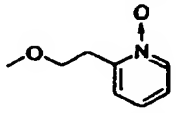
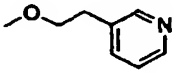
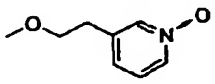
Compound No	X	R1	R2	R3	R4	R5
659	H	Me		Me	Me	
660	H	Me		Me	Me	
661	H	Me		Me	Me	
662	H	Me		Me	Me	
663	H	Me		Me	Me	
664	H	Me		Me	Me	
665	H	Me		Me	Me	
666	H	Me		Me	Me	
667	H	Me		Me	Me	
668	H	Me		Me	Me	
669	H	Me		Me	Me	
670	H	Me		Me	Me	
671	H	Me		Me	Me	
672	H	Me		Me	Me	

Table 1 (continued)

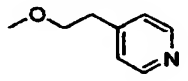
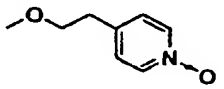
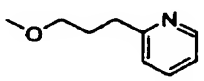
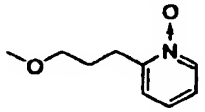
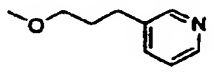
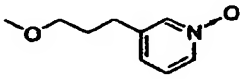
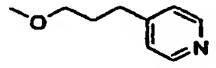
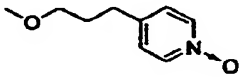
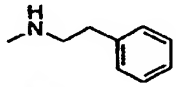
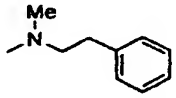
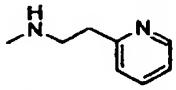
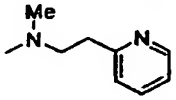
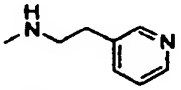
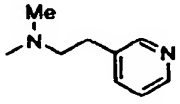
Compound No	X	R1	R2	R3	R4	R5
673	H	Me		Me	Me	
674	H	Me		Me	Me	
675	H	Me		Me	Me	
676	H	Me		Me	Me	
677	H	Me		Me	Me	
678	H	Me		Me	Me	
679	H	Me		Me	Me	
680	H	Me		Me	Me	
681	H	Me		Me	Me	
682	H	Me		Me	Me	
683	H	Me		Me	Me	
684	H	Me		Me	Me	
685	H	Me		Me	Me	
686	H	Me		Me	Me	

Table 1 (continued)

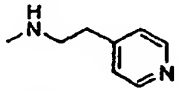
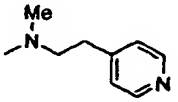
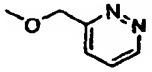
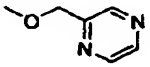
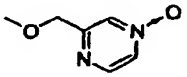
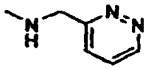
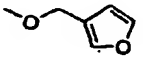
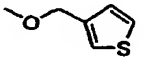
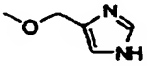
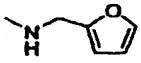
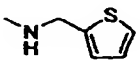
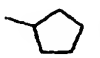
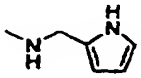
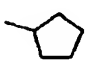
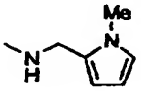
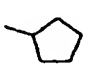
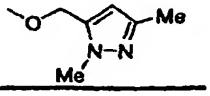
Compound No	X	R1	R2	R3	R4	R5
687	H	Me		Me	Me	
688	H	Me		Me	Me	
689	H	Me		Me	Me	
690	H	Me		Me	Me	
691	H	Me		Me	Me	
692	H	Me		Me	Me	
693	H	Me		Me	Me	
694	H	Me		Me	Me	
695	H	Me		Me	Me	
696	H	Me		Me	Me	
697	H	Me		Me	Me	
698	H	Me		Me	Me	
699	H	Me		Me	Me	
700	H	Me		Me	Me	

Table 1 (continued)

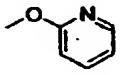
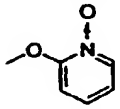
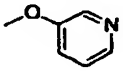
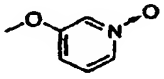
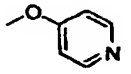
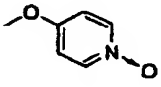
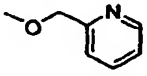
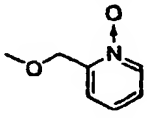
Compound No	X	R1	R2	R3	R4	R5
701	H	Me		Me	Et	H
702	H	Me		Me	Et	OMe
703	H	Me		Me	Et	F
704	H	Me		Me	Et	Cl
705	H	Me		Me	Et	Br
706	H	Me		Me	Et	I
707	H	Me		Me	Et	
708	H	Me		Me	Et	
709	H	Me		Me	Et	
710	H	Me		Me	Et	
711	H	Me		Me	Et	
712	H	Me		Me	Et	
713	H	Me		Me	Et	
714	H	Me		Me	Et	

Table 1 (continued)

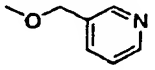
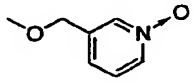
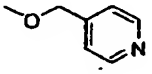
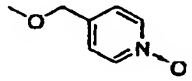
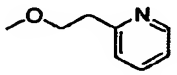
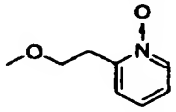
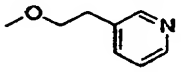
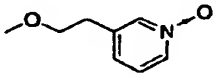
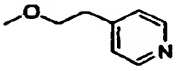
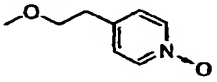
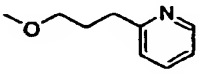
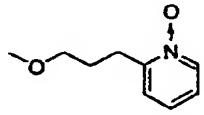
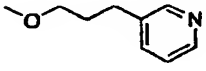
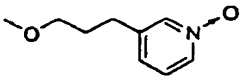
Compound No	X	R1	R2	R3	R4	R5
715	H	Me		Me	Et	
716	H	Me		Me	Et	
717	H	Me		Me	Et	
718	H	Me		Me	Et	
719	H	Me		Me	Et	
720	H	Me		Me	Et	
721	H	Me		Me	Et	
722	H	Me		Me	Et	
723	H	Me		Me	Et	
724	H	Me		Me	Et	
725	H	Me		Me	Et	
726	H	Me		Me	Et	
727	H	Me		Me	Et	
728	H	Me		Me	Et	

Table 1 (continued)

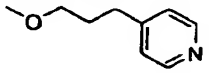
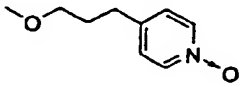
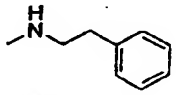
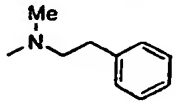
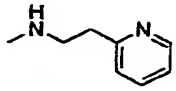
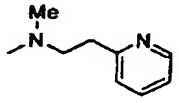
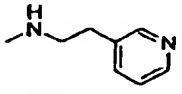
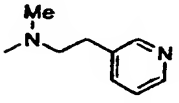
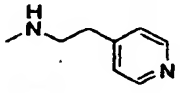
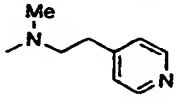
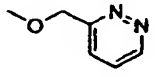
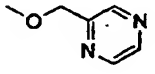
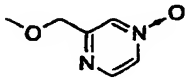
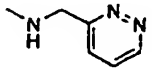
Compound No	X	R1	R2	R3	R4	R5
729	H	Me		Me	Et	
730	H	Me		Me	Et	
731	H	Me		Me	Et	
732	H	Me		Me	Et	
733	H	Me		Me	Et	
734	H	Me		Me	Et	
735	H	Me		Me	Et	
736	H	Me		Me	Et	
737	H	Me		Me	Et	
738	H	Me		Me	Et	
739	H	Me		Me	Et	
740	H	Me		Me	Et	
741	H	Me		Me	Et	
742	H	Me		Me	Et	

Table 1 (continued)

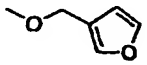
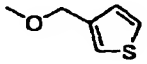
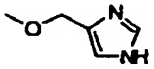
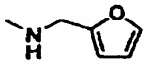
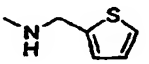
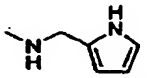
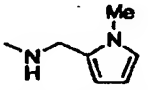
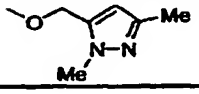
Compound No	X	R1	R2	R3	R4	R5
743	H	Me		Me	Et	
744	H	Me		Me	Et	
745	H	Me		Me	Et	
746	H	Me		Me	Et	
747	H	Me		Me	Et	
748	H	Me		Me	Et	
749	H	Me		Me	Et	
750	H	Me		Me	Et	
751	H	Me		Me	OMe	H
752	H	Me		Me	OMe	OMe
753	H	Me		Me	OMe	F
754	H	Me		Me	OMe	Cl
755	H	Me		Me	OMe	Br
756	H	Me		Me	OMe	I

Table 1 (continued)

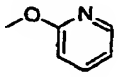
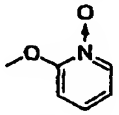
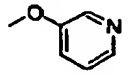
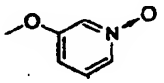
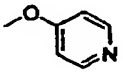
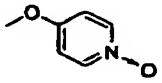
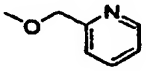
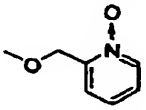
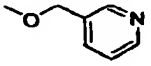
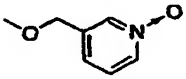
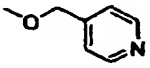
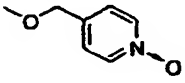
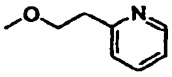
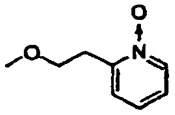
Compound No	X	R1	R2	R3	R4	R5
757	H	Me		Me	OMe	
758	H	Me		Me	OMe	
759	H	Me		Me	OMe	
760	H	Me		Me	OMe	
761	H	Me		Me	OMe	
762	H	Me		Me	OMe	
763	H	Me		Me	OMe	
764	H	Me		Me	OMe	
765	H	Me		Me	OMe	
766	H	Me		Me	OMe	
767	H	Me		Me	OMe	
768	H	Me		Me	OMe	
769	H	Me		Me	OMe	
770	H	Me		Me	OMe	

Table 1 (continued)

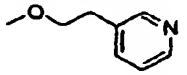
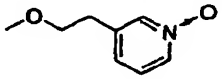
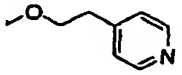
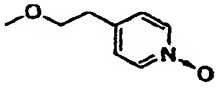
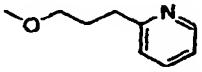
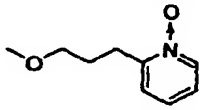
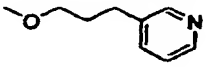
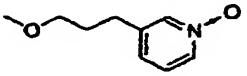
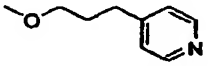
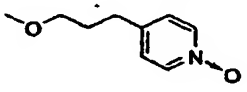
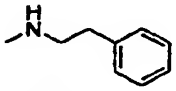
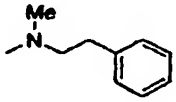
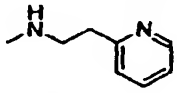
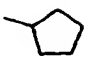
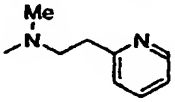
Compound No	X	R1	R2	R3	R4	R5
771	H	Me		Me	OMe	
772	H	Me		Me	OMe	
773	H	Me		Me	OMe	
774	H	Me		Me	OMe	
775	H	Me		Me	OMe	
776	H	Me		Me	OMe	
777	H	Me		Me	OMe	
778	H	Me		Me	OMe	
779	H	Me		Me	OMe	
780	H	Me		Me	OMe	
781	H	Me		Me	OMe	
782	H	Me		Me	OMe	
783	H	Me		Me	OMe	
784	H	Me		Me	OMe	

Table 1 (continued)

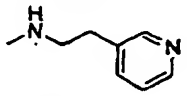
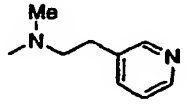
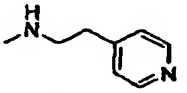
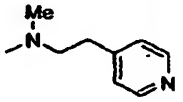
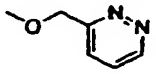
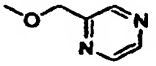
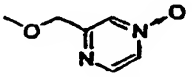
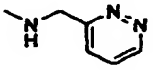
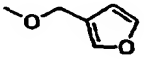
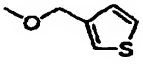
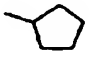
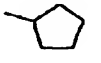
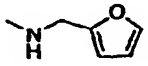
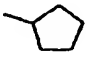
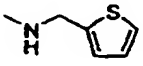
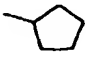
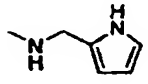
Compound No	X	R1	R2	R3	R4	R5
785	H	Me		Me	OMe	
786	H	Me		Me	OMe	
787	H	Me		Me	OMe	
788	H	Me		Me	OMe	
789	H	Me		Me	OMe	
790	H	Me		Me	OMe	
791	H	Me		Me	OMe	
792	H	Me		Me	OMe	
793	H	Me		Me	OMe	
794	H	Me		Me	OMe	
795	H	Me		Me	OMe	
796	H	Me		Me	OMe	
797	H	Me		Me	OMe	
798	H	Me		Me	OMe	

Table 1 (continued)

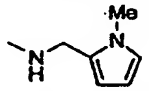
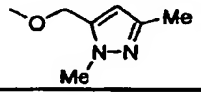
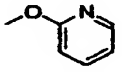
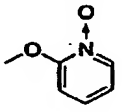
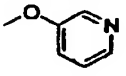
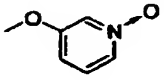
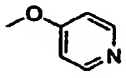
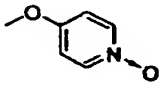
Compound No	X	R1	R2	R3	R4	R5
799	H	Me		Me	OMe	
800	H	Me		Me	OMe	
801	H	Me		Me	NH_2	H
802	H	Me		Me	NH_2	OMe
803	H	Me		Me	NH_2	F
804	H	Me		Me	NH_2	Cl
805	H	Me		Me	NH_2	Br
806	H	Me		Me	NH_2	I
807	H	Me		Me	NH_2	
808	H	Me		Me	NH_2	
809	H	Me		Me	NH_2	
810	H	Me		Me	NH_2	
811	H	Me		Me	NH_2	
812	H	Me		Me	NH_2	

Table 1 (continued)

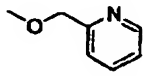
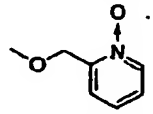
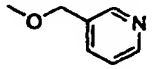
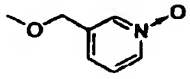
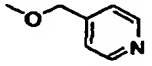
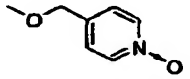
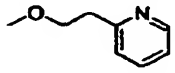
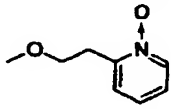
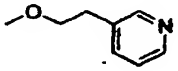
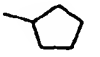
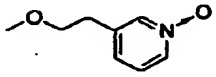
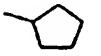
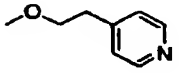
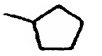
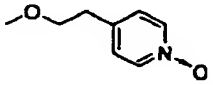
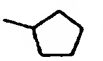
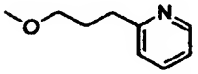
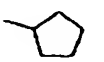
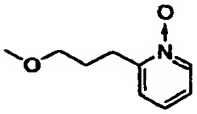
Compound No	X	R1	R2	R3	R4	R5
813	H	Me		Me	NH_2	
814	H	Me		Me	NH_2	
815	H	Me		Me	NH_2	
816	H	Me		Me	NH_2	
817	H	Me		Me	NH_2	
818	H	Me		Me	NH_2	
819	H	Me		Me	NH_2	
820	H	Me		Me	NH_2	
821	H	Me		Me	NH_2	
822	H	Me		Me	NH_2	
823	H	Me		Me	NH_2	
824	H	Me		Me	NH_2	
825	H	Me		Me	NH_2	
826	H	Me		Me	NH_2	

Table 1 (continued)

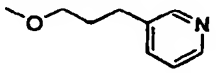
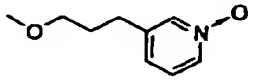
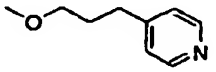
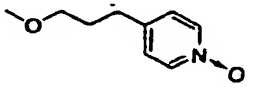
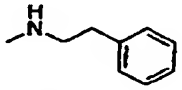
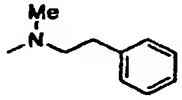
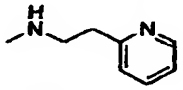
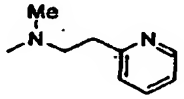
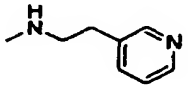
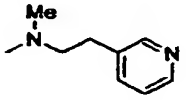
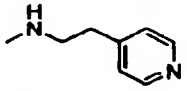
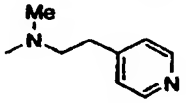
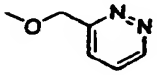
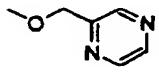
Compound No	X	R1	R2	R3	R4	R5
827	H	Me		Me	NH_2	
828	H	Me		Me	NH_2	
829	H	Me		Me	NH_2	
830	H	Me		Me	NH_2	
831	H	Me		Me	NH_2	
832	H	Me		Me	NH_2	
833	H	Me		Me	NH_2	
834	H	Me		Me	NH_2	
835	H	Me		Me	NH_2	
836	H	Me		Me	NH_2	
837	H	Me		Me	NH_2	
838	H	Me		Me	NH_2	
839	H	Me		Me	NH_2	
840	H	Me		Me	NH_2	

Table 1 (continued)

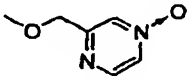
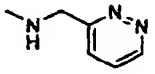
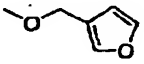
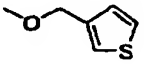
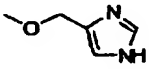
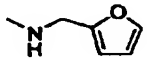
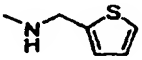
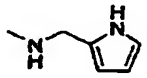
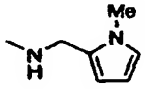
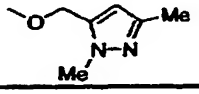
Compound No	X	R1	R2	R3	R4	R5
841	H	Me		Me	NH_2	
842	H	Me		Me	NH_2	
843	H	Me		Me	NH_2	
844	H	Me		Me	NH_2	
845	H	Me		Me	NH_2	
846	H	Me		Me	NH_2	
847	H	Me		Me	NH_2	
848	H	Me		Me	NH_2	
849	H	Me		Me	NH_2	
850	H	Me		Me	NH_2	
851	H	Me		Me	NHMe	H
852	H	Me		Me	NHMe	OMe
853	H	Me		Me	NHMe	F
854	H	Me		Me	NHMe	Cl

Table 1 (continued)

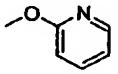
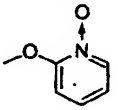
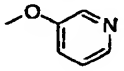
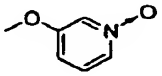
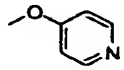
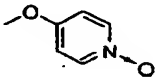
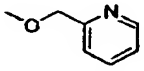
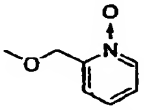
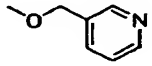
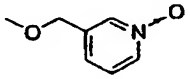
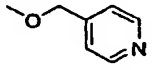
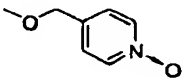
Compound No	X	R1	R2	R3	R4	R5
855	H	Me		Me	NHMe	Br
856	H	Me		Me	NHMe	I
857	H	Me		Me	NHMe	
858	H	Me		Me	NHMe	
859	H	Me		Me	NHMe	
860	H	Me		Me	NHMe	
861	H	Me		Me	NHMe	
862	H	Me		Me	NHMe	
863	H	Me		Me	NHMe	
864	H	Me		Me	NHMe	
865	H	Me		Me	NHMe	
866	H	Me		Me	NHMe	
867	H	Me		Me	NHMe	
868	H	Me		Me	NHMe	

Table 1 (continued)

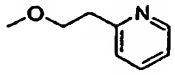
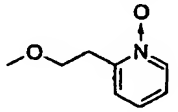
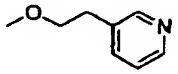
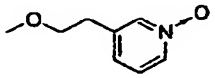
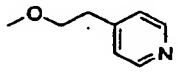
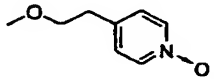
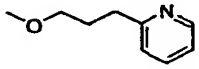
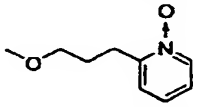
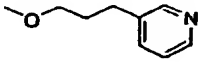
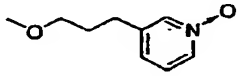
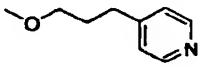
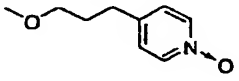
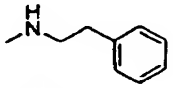
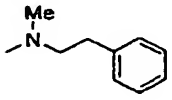
Compound No	X	R1	R2	R3	R4	R5
869	H	Me		Me	NHMe	
870	H	Me		Me	NHMe	
871	H	Me		Me	NHMe	
872	H	Me		Me	NHMe	
873	H	Me		Me	NHMe	
874	H	Me		Me	NHMe	
875	H	Me		Me	NHMe	
876	H	Me		Me	NHMe	
877	H	Me		Me	NHMe	
878	H	Me		Me	NHMe	
879	H	Me		Me	NHMe	
880	H	Me		Me	NHMe	
881	H	Me		Me	NHMe	
882	H	Me		Me	NHMe	

Table 1 (continued)

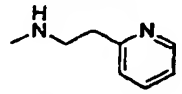
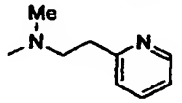
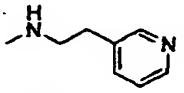
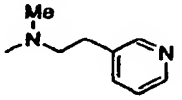
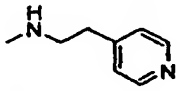
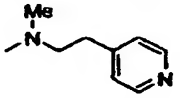
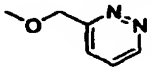
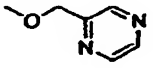
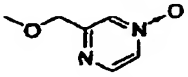
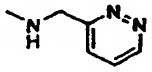
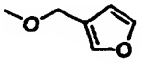
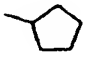
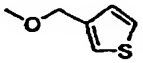
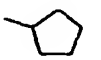
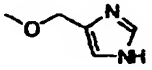
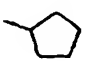
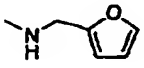
Compound No	X	R1	R2	R3	R4	R5
883	H	Me		Me	NHMe	
884	H	Me		Me	NHMe	
885	H	Me		Me	NHMe	
886	H	Me		Me	NHMe	
887	H	Me		Me	NHMe	
888	H	Me		Me	NHMe	
889	H	Me		Me	NHMe	
890	H	Me		Me	NHMe	
891	H	Me		Me	NHMe	
892	H	Me		Me	NHMe	
893	H	Me		Me	NHMe	
894	H	Me		Me	NHMe	
895	H	Me		Me	NHMe	
896	H	Me		Me	NHMe	

Table 1 (continued)

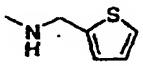
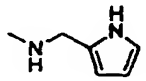
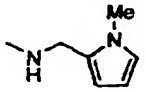
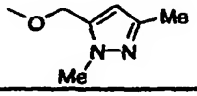
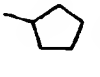
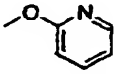
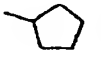
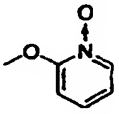
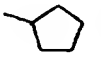
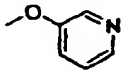
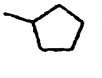
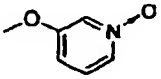
Compound No	X	R1	R2	R3	R4	R5
897	H	Me		Me	NHMe	
898	H	Me		Me	NHMe	
899	H	Me		Me	NHMe	
900	H	Me		Me	NHMe	
901	H	Me		Me	NHEt	H
902	H	Me		Me	NHEt	OMe
903	H	Me		Me	NHEt	F
904	H	Me		Me	NHEt	Cl
905	H	Me		Me	NHEt	Br
906	H	Me		Me	NHEt	I
907	H	Me		Me	NHEt	
908	H	Me		Me	NHEt	
909	H	Me		Me	NHEt	
910	H	Me		Me	NHEt	

Table 1 (continued)

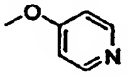
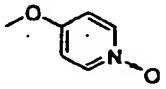
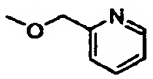
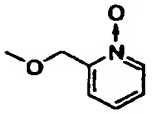
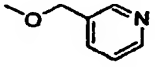
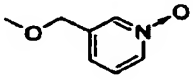
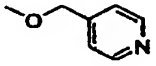
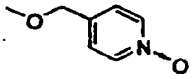
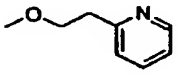
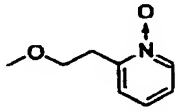
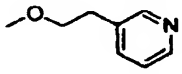
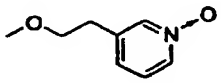
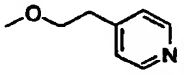
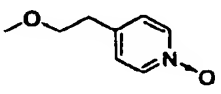
Compound No	X	R1	R2	R3	R4	R5
911	H	Me		Me	NHEt	
912	H	Me		Me	NHEt	
913	H	Me		Me	NHEt	
914	H	Me		Me	NHEt	
915	H	Me		Me	NHEt	
916	H	Me		Me	NHEt	
917	H	Me		Me	NHEt	
918	H	Me		Me	NHEt	
919	H	Me		Me	NHEt	
920	H	Me		Me	NHEt	
921	H	Me		Me	NHEt	
922	H	Me		Me	NHEt	
923	H	Me		Me	NHEt	
924	H	Me		Me	NHEt	

Table 1 (continued)

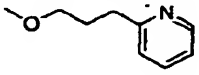
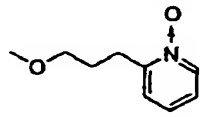
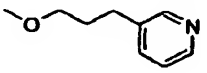
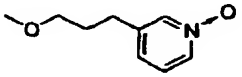
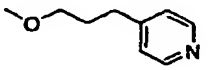
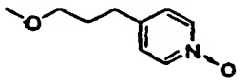
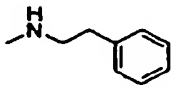
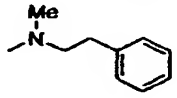
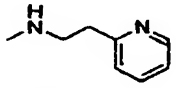
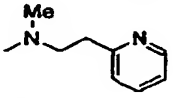
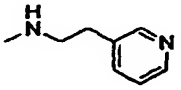
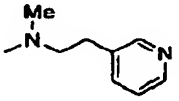
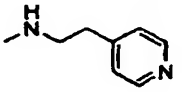
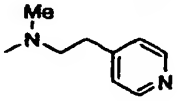
Compound No	X	R1	R2	R3	R4	R5
925	H	Me		Me	NHEt	
926	H	Me		Me	NHEt	
927	H	Me		Me	NHEt	
928	H	Me		Me	NHEt	
929	H	Me		Me	NHEt	
930	H	Me		Me	NHEt	
931	H	Me		Me	NHEt	
932	H	Me		Me	NHEt	
933	H	Me		Me	NHEt	
934	H	Me		Me	NHEt	
935	H	Me		Me	NHEt	
936	H	Me		Me	NHEt	
937	H	Me		Me	NHEt	
938	H	Me		Me	NHEt	

Table 1 (continued)

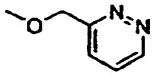
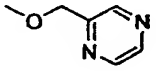
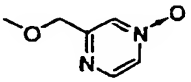
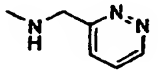
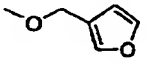
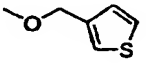
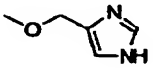
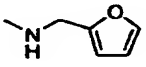
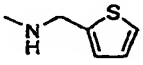
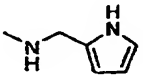
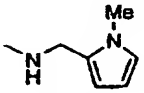
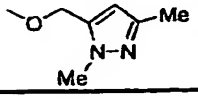
Compound No	X	R1	R2	R3	R4	R5
939	H	Me		Me	NHEt	
940	H	Me		Me	NHEt	
941	H	Me		Me	NHEt	
942	H	Me		Me	NHEt	
943	H	Me		Me	NHEt	
944	H	Me		Me	NHEt	
945	H	Me		Me	NHEt	
946	H	Me		Me	NHEt	
947	H	Me		Me	NHEt	
948	H	Me		Me	NHEt	
949	H	Me		Me	NHEt	
950	H	Me		Me	NHEt	
951	H	Me		Me	NH*n*-Pr	H
952	H	Me		Me	NH*n*-Pr	OMe

Table 1 (continued)

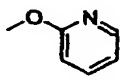
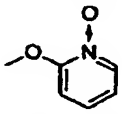
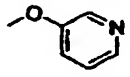
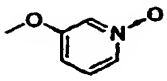
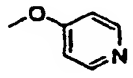
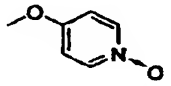
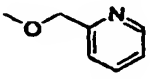
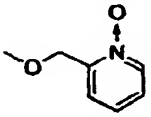
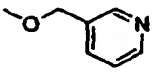
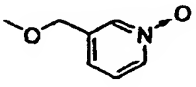
Compound No	X	R1	R2	R3	R4	R5
953	H	Me		Me	NH*n*-Pr	F
954	H	Me		Me	NH*n*-Pr	Cl
955	H	Me		Me	NH*n*-Pr	Br
956	H	Me		Me	NH*n*-Pr	I
957	H	Me		Me	NH*n*-Pr	
958	H	Me		Me	NH*n*-Pr	
959	H	Me		Me	NH*n*-Pr	
960	H	Me		Me	NH*n*-Pr	
961	H	Me		Me	NH*n*-Pr	
962	H	Me		Me	NH*n*-Pr	
963	H	Me		Me	NH*n*-Pr	
964	H	Me		Me	NH*n*-Pr	
965	H	Me		Me	NH*n*-Pr	
966	H	Me		Me	NH*n*-Pr	

Table 1 (continued)

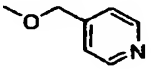
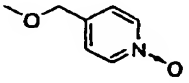
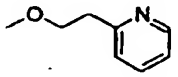
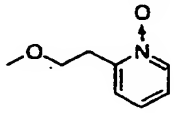
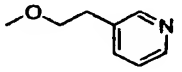
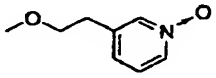
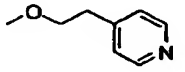
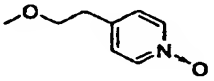
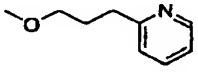
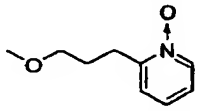
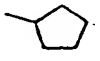
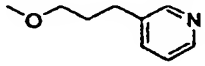
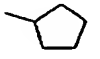
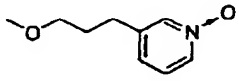
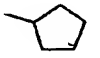
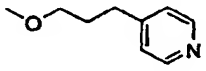
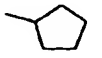
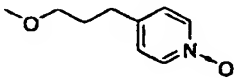
Compound No	X	R1	R2	R3	R4	R5
967	H	Me		Me	NH*n*-Pr	
968	H	Me		Me	NH*n*-Pr	
969	H	Me		Me	NH*n*-Pr	
970	H	Me		Me	NH*n*-Pr	
971	H	Me		Me	NH*n*-Pr	
972	H	Me		Me	NH*n*-Pr	
973	H	Me		Me	NH*n*-Pr	
974	H	Me		Me	NH*n*-Pr	
975	H	Me		Me	NH*n*-Pr	
976	H	Me		Me	NH*n*-Pr	
977	H	Me		Me	NH*n*-Pr	
978	H	Me		Me	NH*n*-Pr	
979	H	Me		Me	NH*n*-Pr	
980	H	Me		Me	NH*n*-Pr	

Table 1 (continued)

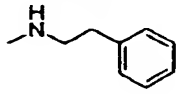
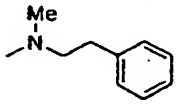
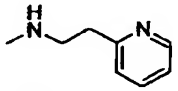
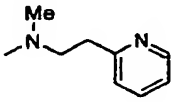
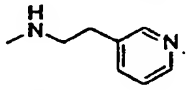
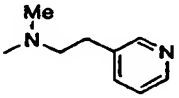
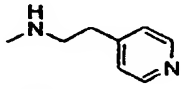
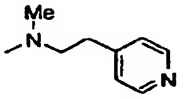
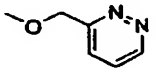
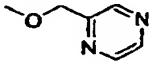
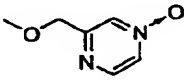
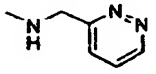
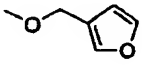
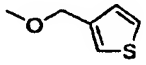
Compound No	X	R1	R2	R3	R4	R5
981	H	Me		Me	NH*n*-Pr	
982	H	Me		Me	NH*n*-Pr	
983	H	Me		Me	NH*n*-Pr	
984	H	Me		Me	NH*n*-Pr	
985	H	Me		Me	NH*n*-Pr	
986	H	Me		Me	NH*n*-Pr	
987	H	Me		Me	NH*n*-Pr	
988	H	Me		Me	NH*n*-Pr	
989	H	Me		Me	NH*n*-Pr	
990	H	Me		Me	NH*n*-Pr	
991	H	Me		Me	NH*n*-Pr	
992	H	Me		Me	NH*n*-Pr	
993	H	Me		Me	NH*n*-Pr	
994	H	Me		Me	NH*n*-Pr	

Table 1 (continued)

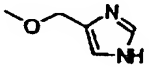
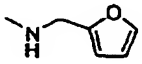
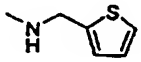
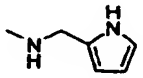
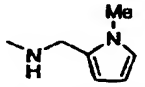
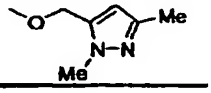
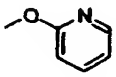
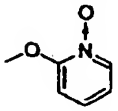
Compound No	X	R1	R2	R3	R4	R5
995	H	Me		Me	NH*n*-Pr	
996	H	Me		Me	NH*n*-Pr	
997	H	Me		Me	NH*n*-Pr	
998	H	Me		Me	NH*n*-Pr	
999	H	Me		Me	NH*n*-Pr	
1000	H	Me		Me	NH*n*-Pr	
1001	H	Me		Me	NMe_2	H
1002	H	Me		Me	NMe_2	OMe
1003	H	Me		Me	NMe_2	F
1004	H	Me		Me	NMe_2	Cl
1005	H	Me		Me	NMe_2	Br
1006	H	Me		Me	NMe_2	I
1007	H	Me		Me	NMe_2	
1008	H	Me		Me	NMe_2	

Table 1 (continued)

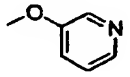
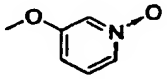
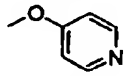
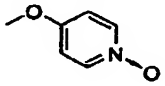
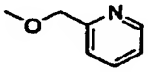
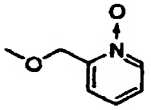
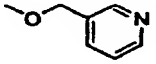
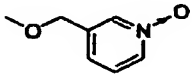
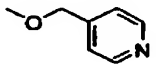
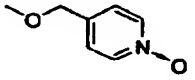
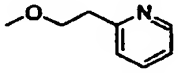
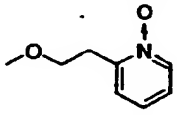
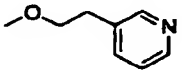
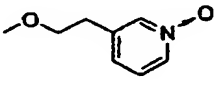
Compound No	X	R1	R2	R3	R4	R5
1009	H	Me		Me	NMe_2	
1010	H	Me		Me	NMe_2	
1011	H	Me		Me	NMe_2	
1012	H	Me		Me	NMe_2	
1013	H	Me		Me	NMe_2	
1014	H	Me		Me	NMe_2	
1015	H	Me		Me	NMe_2	
1016	H	Me		Me	NMe_2	
1017	H	Me		Me	NMe_2	
1018	H	Me		Me	NMe_2	
1019	H	Me		Me	NMe_2	
1020	H	Me		Me	NMe_2	
1021	H	Me		Me	NMe_2	
1022	H	Me		Me	NMe_2	

Table 1 (continued)

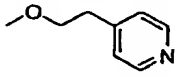
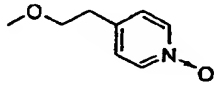
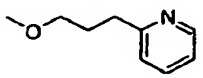
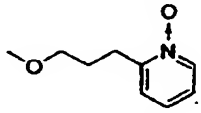
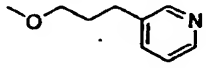
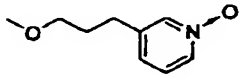
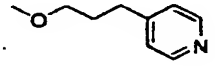
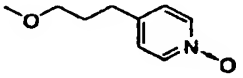
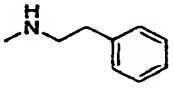
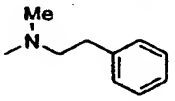
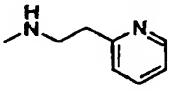
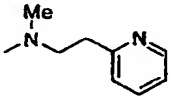
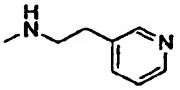
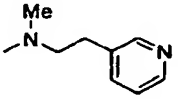
Compound No	X	R1	R2	R3	R4	R5
1023	H	Me		Me	NMe_2	
1024	H	Me		Me	NMe_2	
1025	H	Me		Me	NMe_2	
1026	H	Me		Me	NMe_2	
1027	H	Me		Me	NMe_2	
1028	H	Me		Me	NMe_2	
1029	H	Me		Me	NMe_2	
1030	H	Me		Me	NMe_2	
1031	H	Me		Me	NMe_2	
1032	H	Me		Me	NMe_2	
1033	H	Me		Me	NMe_2	
1034	H	Me		Me	NMe_2	
1035	H	Me		Me	NMe_2	
1036	H	Me		Me	NMe_2	

Table 1 (continued)

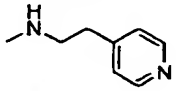
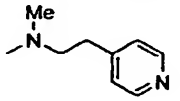
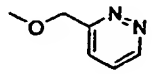
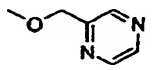
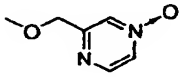
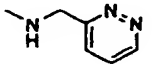
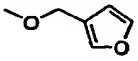
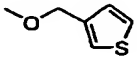
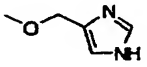
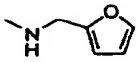
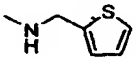
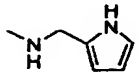
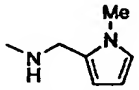
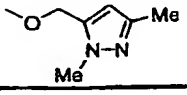
Compound No	X	R1	R2	R3	R4	R5
1037	H	Me		Me	NMe_2	
1038	H	Me		Me	NMe_2	
1039	H	Me		Me	NMe_2	
1040	H	Me		Me	NMe_2	
1041	H	Me		Me	NMe_2	
1042	H	Me		Me	NMe_2	
1043	H	Me		Me	NMe_2	
1044	H	Me		Me	NMe_2	
1045	H	Me		Me	NMe_2	
1046	H	Me		Me	NMe_2	
1047	H	Me		Me	NMe_2	
1048	H	Me		Me	NMe_2	
1049	H	Me		Me	NMe_2	
1050	H	Me		Me	NMe_2	

Table 1 (continued)

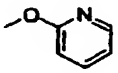
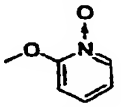
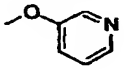
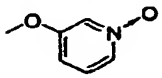
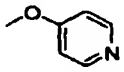
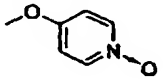
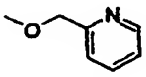
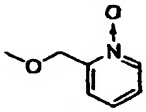
Compound No	X	R1	R2	R3	R4	R5
1051	H	Me		Me	Cl	H
1052	H	Me		Me	Cl	OMe
1053	H	Me		Me	Cl	F
1054	H	Me		Me	Cl	Cl
1055	H	Me		Me	Cl	Br
1056	H	Me		Me	Cl	I
1057	H	Me		Me	Cl	
1058	H	Me		Me	Cl	
1059	H	Me		Me	Cl	
1060	H	Me		Me	Cl	
1061	H	Me		Me	Cl	
1062	H	Me		Me	Cl	
1063	H	Me		Me	Cl	
1064	H	Me		Me	Cl	

Table 1 (continued)

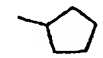
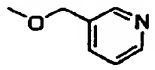
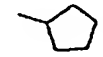
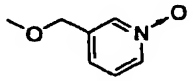
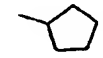
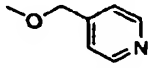
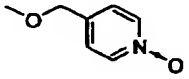
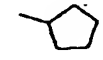
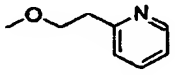
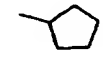
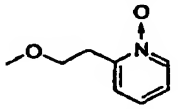
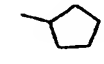
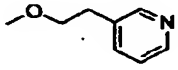
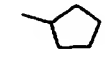
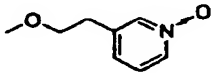
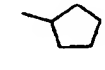
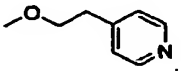
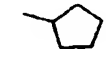
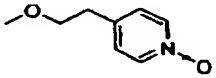
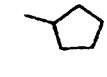
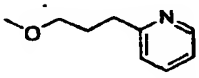
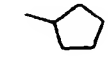
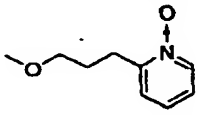
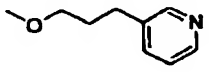
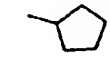
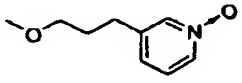
Compound No	X	R1	R2	R3	R4	R5
1065	H	Me		Me	Cl	
1066	H	Me		Me	Cl	
1067	H	Me		Me	Cl	
1068	H	Me		Me	Cl	
1069	H	Me		Me	Cl	
1070	H	Me		Me	Cl	
1071	H	Me		Me	Cl	
1072	H	Me		Me	Cl	
1073	H	Me		Me	Cl	
1074	H	Me		Me	Cl	
1075	H	Me		Me	Cl	
1076	H	Me		Me	Cl	
1077	H	Me		Me	Cl	
1078	H	Me		Me	Cl	

Table 1 (continued)

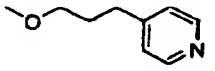
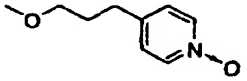
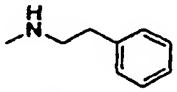
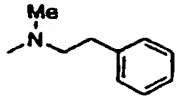
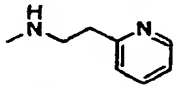
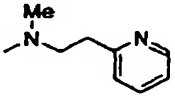
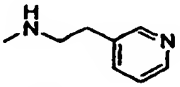
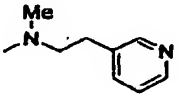
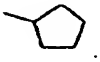
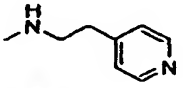
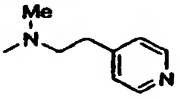
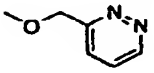
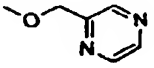
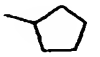
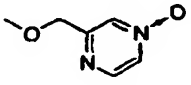
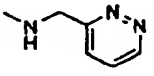
Compound No	X	R1	R2	R3	R4	R5
1079	H	Me		Me	Cl	
1080	H	Me		Me	Cl	
1081	H	Me		Me	Cl	
1082	H	Me		Me	Cl	
1083	H	Me		Me	Cl	
1084	H	Me		Me	Cl	
1085	H	Me		Me	Cl	
1086	H	Me		Me	Cl	
1087	H	Me		Me	Cl	
1088	H	Me		Me	Cl	
1089	H	Me		Me	Cl	
1090	H	Me		Me	Cl	
1091	H	Me		Me	Cl	
1092	H	Me		Me	Cl	

Table 1 (continued)

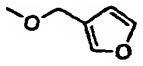
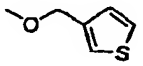
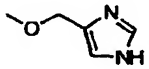
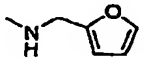
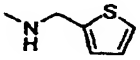
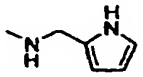
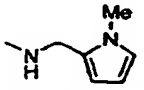
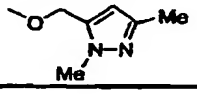
Compound No	X	R1	R2	R3	R4	R5
1093	H	Me		Me	Cl	
1094	H	Me		Me	Cl	
1095	H	Me		Me	Cl	
1096	H	Me		Me	Cl	
1097	H	Me		Me	Cl	
1098	H	Me		Me	Cl	
1099	H	Me		Me	Cl	
1100	H	Me		Me	Cl	
1101	H	Me		Me		H
1102	H	Me		Me		OMe
1103	H	Me		Me		F
1104	H	Me		Me		Cl
1105	H	Me		Me		Br
1106	H	Me		Me		I

Table 1 (continued)

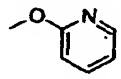
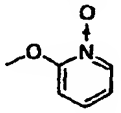
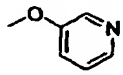
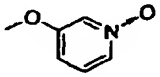
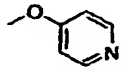
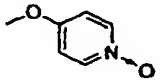
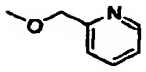
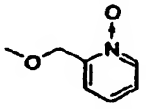
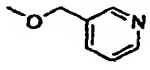
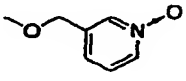
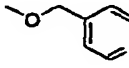
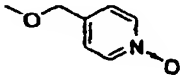
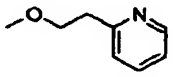
Compound No	X	R1	R2	R3	R4	R5
1107	H	Me		Me		
1108	H	Me		Me		
1109	H	Me		Me		
1110	H	Me		Me		
1111	H	Me		Me		
1112	H	Me		Me		
1113	H	Me		Me		
1114	H	Me		Me		
1115	H	Me		Me		
1116	H	Me		Me		
1117	H	Me		Me		
1118	H	Me		Me		
1119	H	Me		Me		
1120	H	Me		Me		

Table 1 (continued)

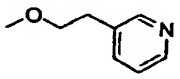
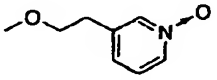
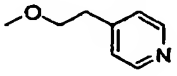
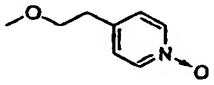
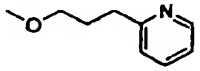
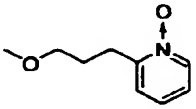
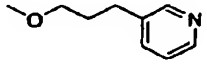
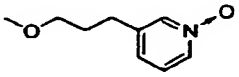
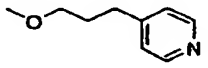
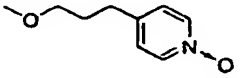
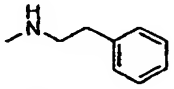
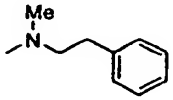
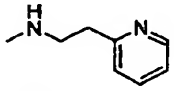
Compound No	X	R1	R2	R3	R4	R5
1121	H	Me		Me		
1122	H	Me		Me		
1123	H	Me		Me		
1124	H	Me		Me		
1125	H	Me		Me		
1126	H	Me		Me		
1127	H	Me		Me		
1128	H	Me		Me		
1129	H	Me		Me		
1130	H	Me		Me		
1131	H	Me		Me		
1132	H	Me		Me		
1133	H	Me		Me		
1134	H	Me		Me		

Table 1 (continued)

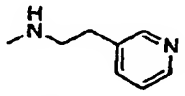
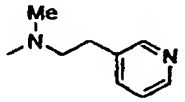
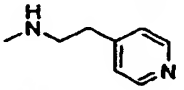
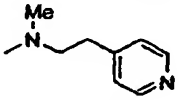
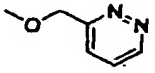
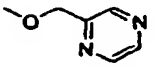
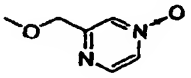
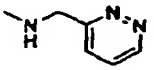
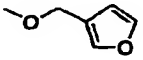
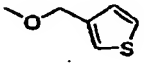
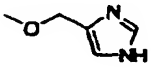
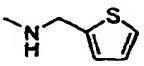
Compound No	X	R1	R2	R3	R4	R5
1135	H	Me		Me		
1136	H	Me		Me		
1137	H	Me		Me		
1138	H	Me		Me		
1139	H	Me		Me		
1140	H	Me		Me		
1141	H	Me		Me		
1142	H	Me		Me		
1143	H	Me		Me		
1144	H	Me		Me		
1145	H	Me		Me		
1146	H	Me		Me		
1147	H	Me		Me		
1148	H	Me		Me		

Table 1 (continued)

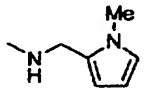
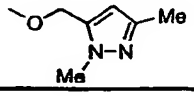
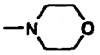
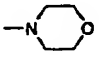
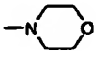
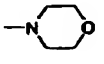
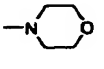
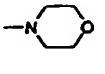
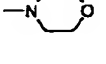
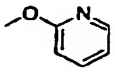
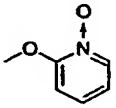
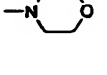
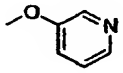
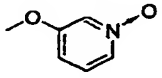
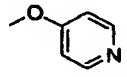
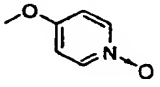
Compound No	X	R1	R2	R3	R4	R5
1149	H	Me		Me		
1150	H	Me		Me		
1151	H	Me		Me		H
1152	H	Me		Me		OMe
1153	H	Me		Me		F
1154	H	Me		Me		Cl
1155	H	Me		Me		Br
1156	H	Me		Me		I
1157	H	Me		Me		
1158	H	Me		Me		
1159	H	Me		Me		
1160	H	Me		Me		
1161	H	Me		Me		
1162	H	Me		Me		

Table 1 (continued)

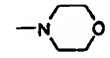
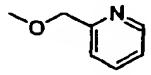
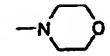
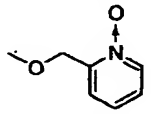
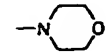
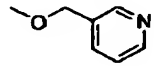
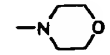
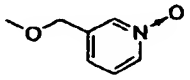
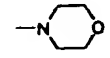
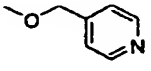
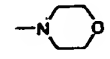
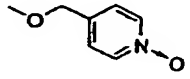
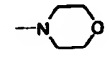
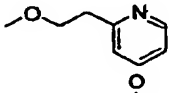
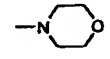
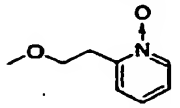
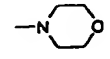
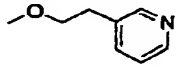
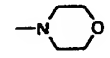
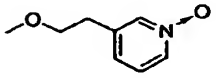
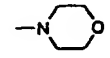
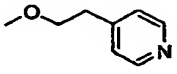
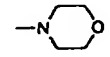
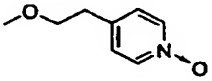
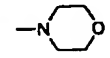
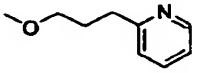
Compound No	X	R1	R2	R3	R4	R5
1163	H	Me		Me		
1164	H	Me		Me		
1165	H	Me		Me		
1166	H	Me		Me		
1167	H	Me		Me		
1168	H	Me		Me		
1169	H	Me		Me		
1170	H	Me		Me		
1171	H	Me		Me		
1172	H	Me		Me		
1173	H	Me		Me		
1174	H	Me		Me		
1175	H	Me		Me		
1176	H	Me		Me		

Table 1 (continued)

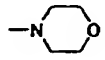
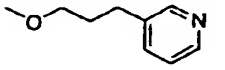
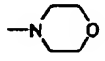
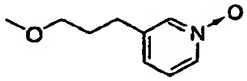
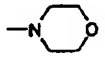
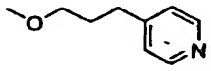
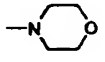
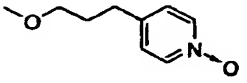
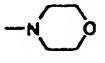
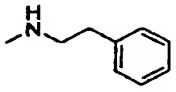
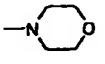
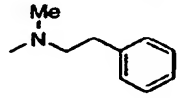
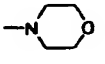
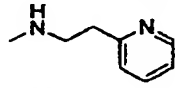
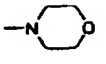
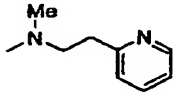
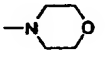
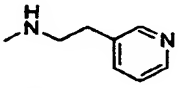
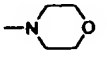
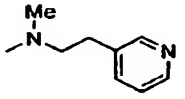
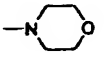
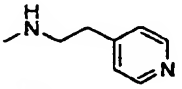
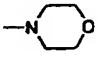
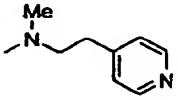
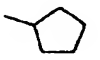
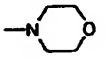
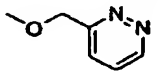
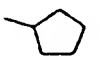
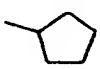
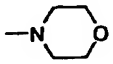
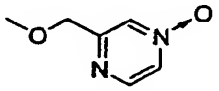
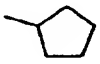
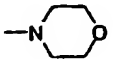
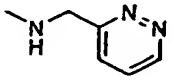
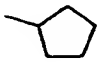
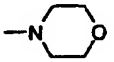
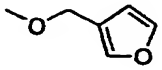
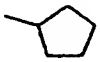
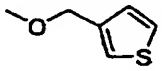
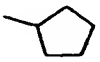
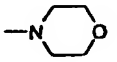
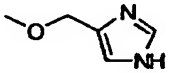
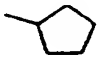
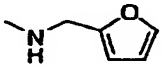
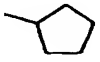
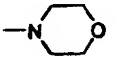
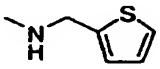
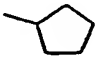
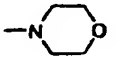
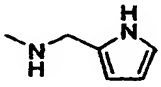
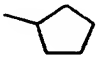
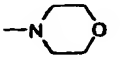
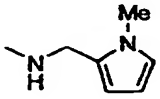
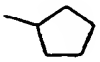
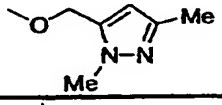
Compound No	X	R1	R2	R3	R4	R5
1177	H	Me		Me		
1178	H	Me		Me		
1179	H	Me		Me		
1180	H	Me		Me		
1181	H	Me		Me		
1182	H	Me		Me		
1183	H	Me		Me		
1184	H	Me		Me		
1185	H	Me		Me		
1186	H	Me		Me		
1187	H	Me		Me		
1188	H	Me		Me		
1189	H	Me		Me		
1190	H	Me		Me		

Table 1 (continued)

Compound No	X	R1	R2	R3	R4	R5
1191	H	Me		Me		
1192	H	Me		Me		
1193	H	Me		Me		
1194	H	Me		Me		
1195	H	Me		Me		
1196	H	Me		Me		
1197	H	Me		Me		
1198	H	Me		Me		
1199	H	Me		Me		
1200	H	Me		Me		

[0024] Examples of particularly preferred compounds of the present invention include the following compounds. However, the compounds of the present invention are not limited to these examples.

2-chloro-9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethylpurine;
9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethyl-2-methoxypurine;
9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethyl-2-(pyridazinylmethyloxy)purine;
9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethyl-2-[4-pyridylmethyloxy]purine;
4-[[9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethylpurin]-2-yl-oxymethyl]pyridine N-oxide;

9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethyl-2-[2-(4-pyridyl)ethyloxy]purine;
4-[[9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethylpurin]-2-yl-2-oxyethyl]pyridine N-oxide;
9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6-methylamino-2-(3-pyridazinylmethyloxy)purine;
9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethyl-2-[2-(4-pyridyl)ethylamino]purine;
9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethyl-2-[(4-pyridyl)methylamino]purine;
9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethyl-2-[3-(4-pyridyl)propyloxy]purine; and
4-[[9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethylpurin]-2-yl-3-oxypropyl]pyridine N-oxide.

[0025] As the salts of the compounds represented by the aforementioned formula (I), physiologically acceptable salts are preferred. Examples include, for example, inorganic acid salts such as hydrochlorides, hydrobromides, hydroiodides, sulfates and phosphates, and organic acid salts such as oxalates, maleates, fumarates, lactates, malates, citrates, tartrates, benzoates, methanesulfonates and p-toluenesulfonates. The compounds of the formula (I), N-oxide derivatives, and salts thereof may exist in the forms of hydrates or solvates, and such hydrates and solvates are also fall within the scope of the present invention. As solvents constituting such solvates, examples include, for example, methanol, ethanol, isopropanol, acetone, ethyl acetate, methylene chloride.

[0026] Among the compounds of the present invention, those wherein R^2 represents tetrahydrofuranyl group or bicyclo[2,2,1]hept-2-yl group may exist as optical enantiomers. Moreover, depending on the types of substituents, they may have one or more asymmetric carbons, and hence stereoisomers such as optical enantiomers and diastereoisomers based on the asymmetric carbon(s) may exist. Any stereoisomers in a pure form, any mixtures thereof, any racemates thereof and the like fall within the scope of the present invention.

[0027] According to the present invention, there are provided the compound represented by the aforementioned formulas (A) and (B). These compounds are useful as synthetic intermediates for the preparation of the aforementioned purine derivatives represented by formula (I). In the compounds represented by the formulas (A) and (B), R^1, R^2 and R^4 have the same meanings as R^1, R^2 and R^4 defined for the compounds of the aforementioned formula (I). R^1 is preferably a C_1-C_4 alkyl group, more preferably a C_1-C_3 alkyl group, further preferably methyl group or ethyl group, and most preferably methyl group. R^2 is preferably tetrahydrofuranyl group, a C_1-C_6 alkyl group, a C_1-C_3 haloalkyl group, or a C_3-C_8 cycloalkyl group, more preferably a C_3-C_8 cycloalkyl group, further preferably a C_4-C_6 cycloalkyl group, and most preferably cyclopentyl group. R^4 is preferably hydrogen atom, a halogen atom, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, a C_1-C_4 alkylamino group, or a C_2-C_8 dialkylamino group, and more preferably a C_1-C_3 alkyl group, a C_1-C_3 alkoxyl group, or a C_1-C_3 alkylamino group. X^2 represents a halogen atom, and preferably chlorine atom.

[0028] Examples of particularly preferred compounds represented by the formula (A) include the following compounds.

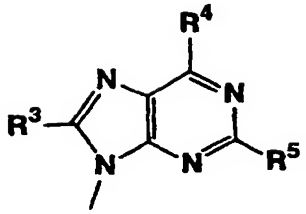
4-(3-cyclopentyloxy-4-methoxybenzylamino)-2-fluoro-5-nitro-6-methylpyrimidine;
2-chloro-4-(3-cyclopentyloxy-4-methoxybenzylamino)-5-nitro-6-methylpyrimidine;
2-bromo-4-(3-cyclopentyloxy-4-methoxybenzylamino)-5-nitro-6-methylpyrimidine; and
4-(3-cyclopentyloxy-4-methoxybenzylamino)-2-iodide-5-nitro-6-methylpyrimidine.

[0029] Examples of particularly preferred compounds represented by the formula (B) include the following compounds.

5-amino-4-(3-cyclopentyloxy-4-methoxybenzylamino)-2-fluoro-6-methylpyrimidine;
5-amino-2-chloro-4-(3-cyclopentyloxy-4-methoxybenzylamino)-6-methylpyrimidine;
5-amino-2-bromo-4-(3-cyclopentyloxy-4-methoxybenzylamino)-6-methylpyrimidine; and
5-amino-4-(3-cyclopentyloxy-4-methoxybenzylamino)-2-iodide-6-methylpyrimidine.

[0030] Methods for preparing the compounds of the present invention are not particularly limited. For example, they can be prepared by the following methods.

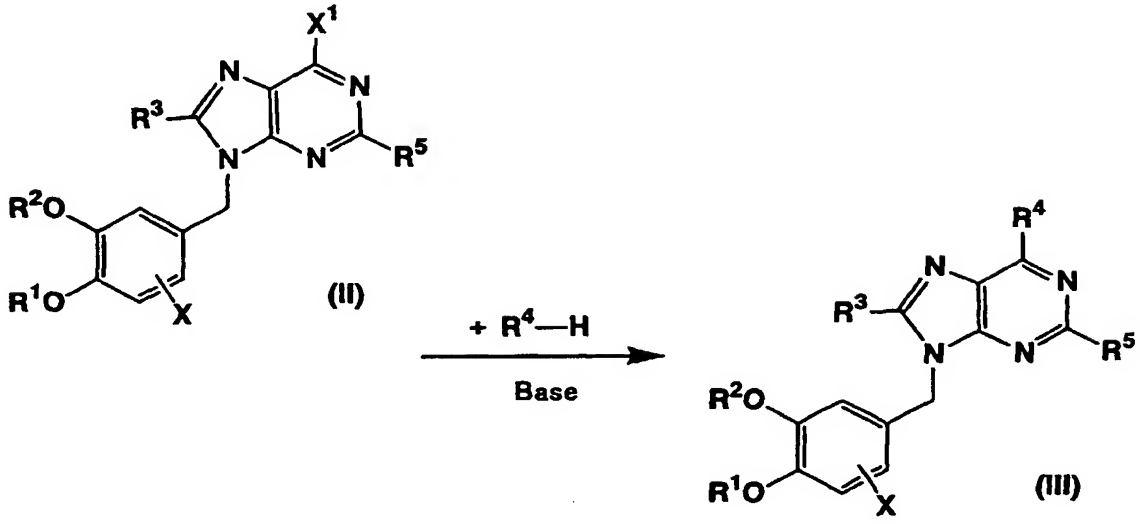
[0031] When A is a group represented by the following formula:



a compound of the following formula (III) can be prepared by the following preparing method 1 or 2.

〈Preparation Method 1〉

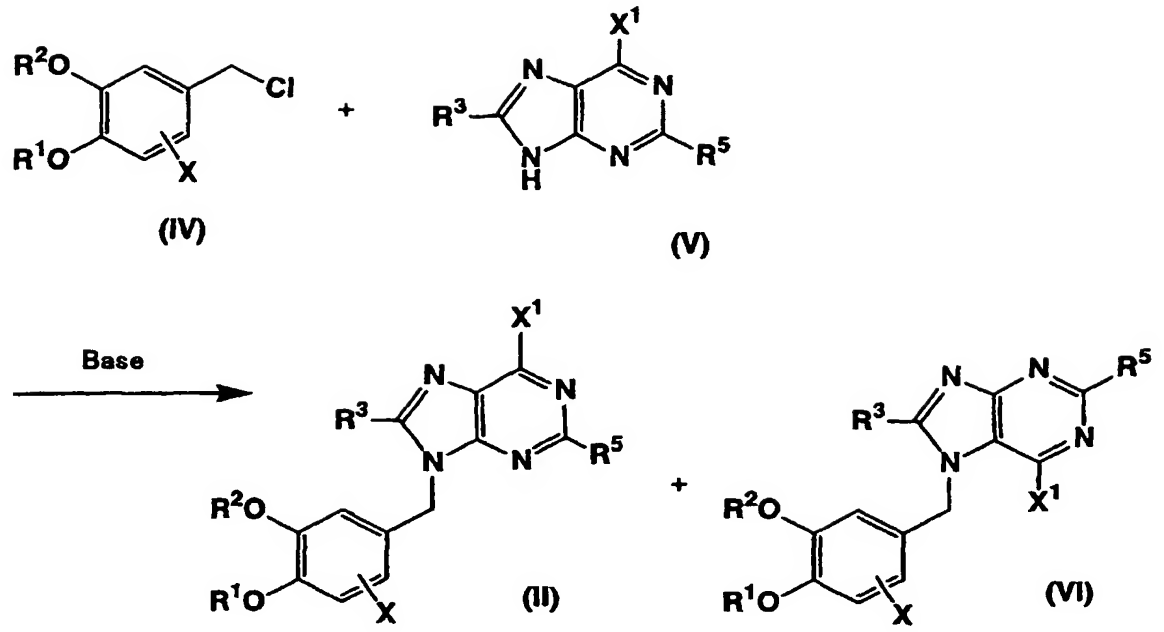
[0032]



[0033] In the scheme, R^1, R^2, R^3, R^4, R^5, and X have the same meanings as those defined above, and X^1 represents a halogen atom.

[0034] The above reaction is performed at a temperature within the range of from 0 to 150°C without a solvent or in a suitable solvent such as N,N-dimethylformamide or tetrahydrofuran, and in the presence or absence of an organic base such as triethylamine, pyridine, and N,N-diethylaniline, or an inorganic base such as sodium carbonate and sodium hydride.

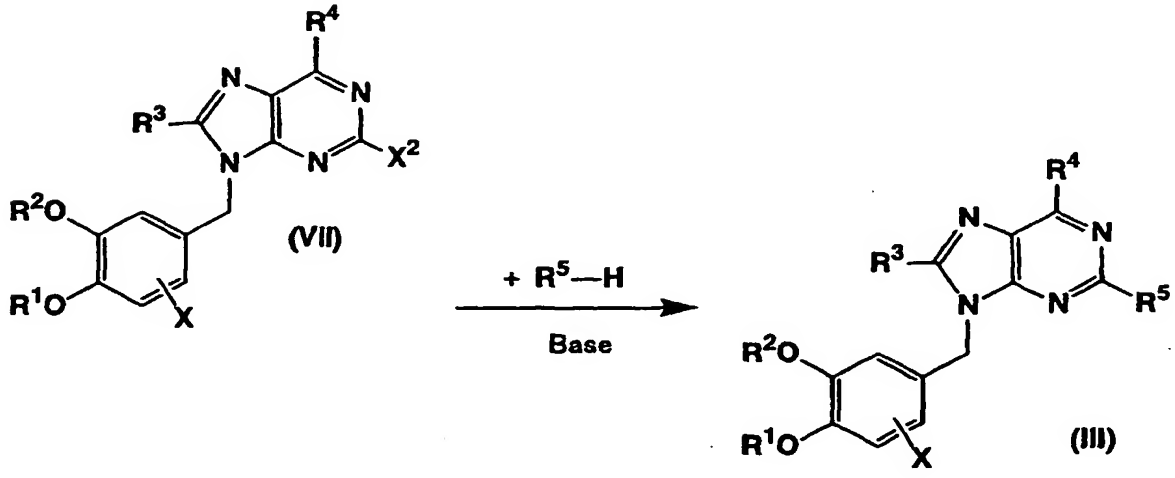
[0035] A compound of the aforementioned formula (II) as the starting material of the above reaction can be prepared according to the following scheme.



[0036] In the scheme, R^1, R^2, R^3, R^4, R^5, X and X^1 have the same meanings as already defined above.

〈Preparation Method 2〉

[0037]



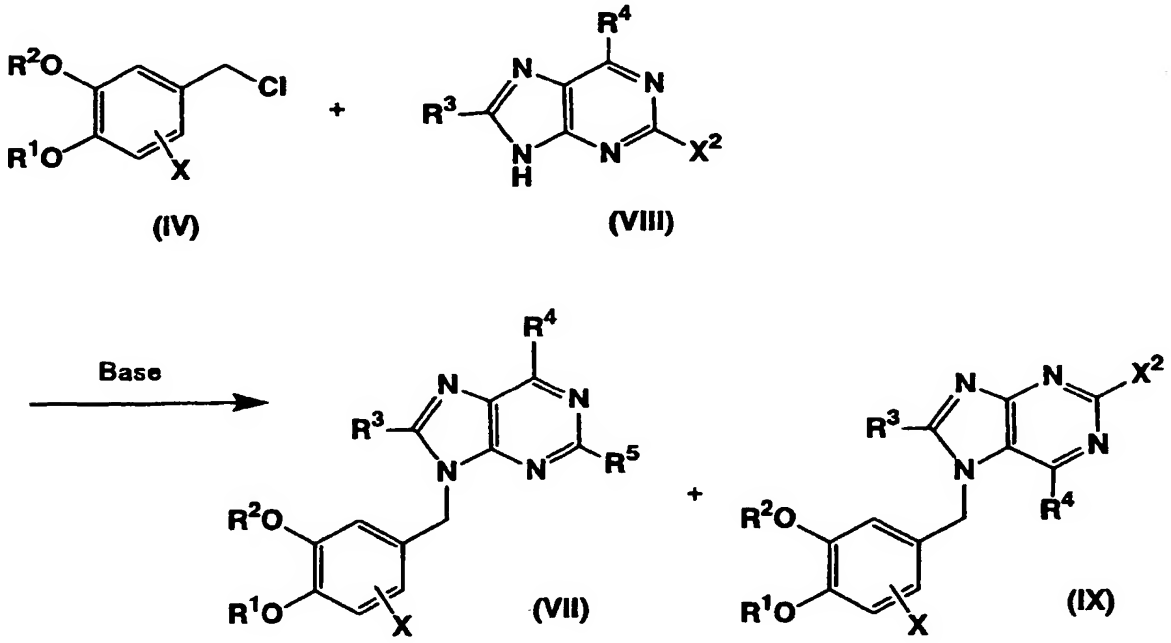
[0038] In the scheme, R^1, R^2, R^3, R^4, R^5, and X have the same meanings as those defined above, and X^2 represents a halogen atom.

[0039] A compound of the formula (III) can be prepared by carrying out condensation of a compound of the formula

(VII) and a compound represented by R^5-H according to the aforementioned reaction. A compound represented by R^5-H is added to a suitable solvent such as N,N-dimethylformamide or tetrahydrofuran or a mixed solvent thereof, and the mixture is added with 1 to 5 equivalents of an organic base such as triethylamine, pyridine or N,N-diethylaniline, or an inorganic base such as sodium carbonate or sodium hydride. Then, the mixture is reacted with a compound of the formula (VII) to obtain the target compound of the formula (III). The reaction is usually performed at from -20 to 150°C under a nitrogen or argon flow. A compound of the aforementioned formula (VII) as the starting material of the aforementioned reaction can be prepared by any one of the following three methods.

Preparation Method (1)

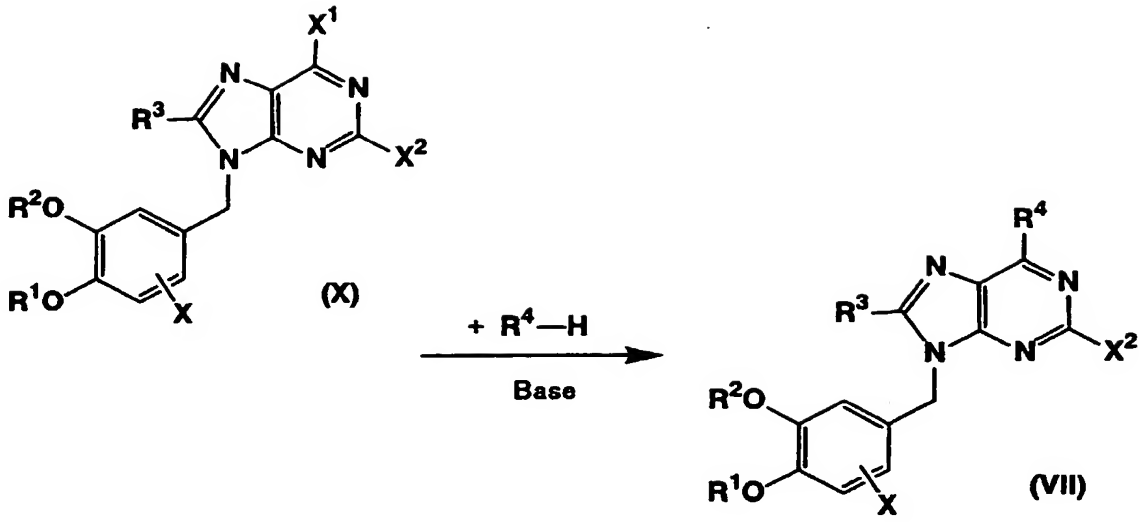
[0040]



[0041] In the scheme, R^1, R^2, R^3, R^4, R^5, X, and X^2 have the same meanings as those defined above.

Preparation Method (2)

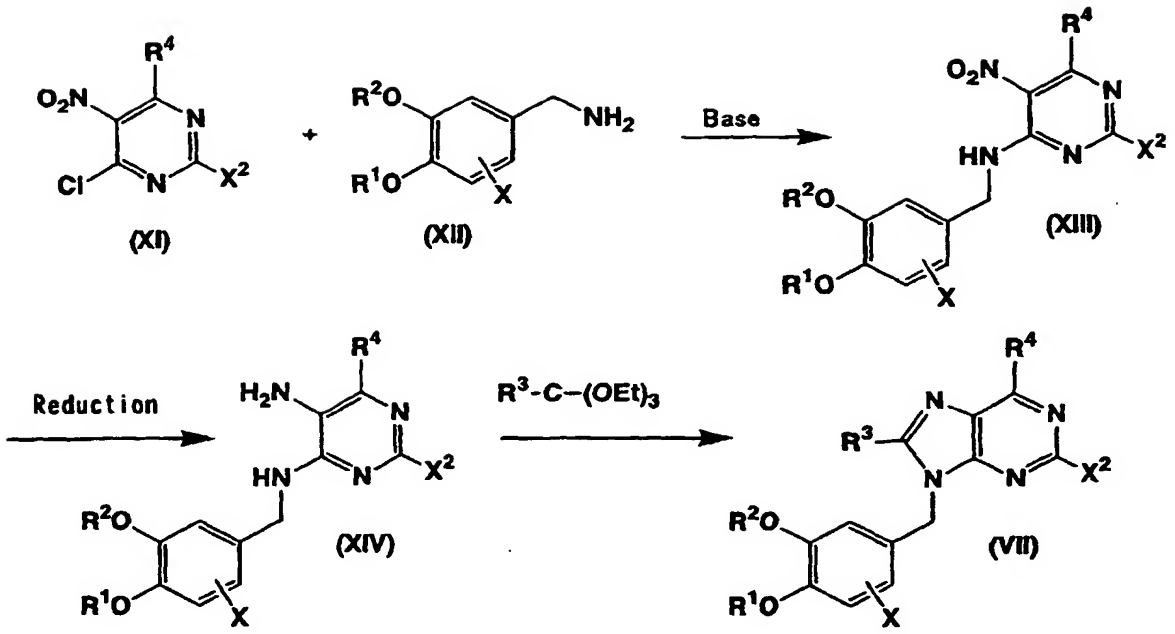
[0042]



[0043] In the scheme, R^1, R^2, R^3, R^4, R^5, X, X^1, and X^2 have the same meanings as those defined above.

Preparation Method (3)

[0044] When X^2 is a halogen atom, a compound of the formula (VII) can also be prepared according to the following reaction formula.



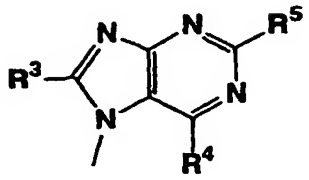
[0045] In the scheme, R^1, R^2, R^3, R^4, R^5, and X have the same meanings as those defined above, and X^2 represents a halogen atom.

[0046] In the above reaction, a compound of the formula (XI) and a compound of the formula (XII) are first condensed to prepare a compound of the formula (XIII). The compound of the formula (XI) and the compound of the formula (XII) are added to a suitable solvent such as N,N-dimethylformamide, tetrahydrofuran, methylene chloride or water, or a mixed solvent comprising a combination of these solvents, and the mixture is then added with 1 to 5 equivalents of an organic base such as triethylamine, pyridine or N,N-diethylaniline, or an inorganic base such as sodium carbonate or sodium hydride to obtain the target compound of the formula (XIII). The reaction is usually performed at -20 to 150°C under a nitrogen or argon flow.

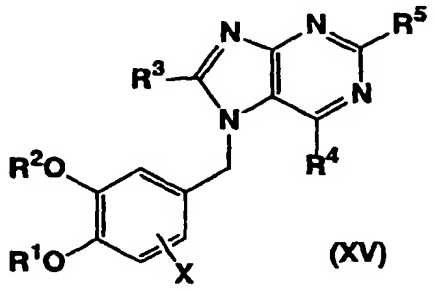
[0047] Then, a compound of the formula (XIV) can be obtained by reducing the compound of the formula (XIII). The reduction can be performed by dissolving the compound of the formula (XIII) in a solvent such as methanol, ethanol or tetrahydrofuran, or a mixed solvent comprising a combination of such solvents, adding 10 to 100% by weight of a catalyst such as Raney Nickel, palladium/carbon, hydroxylated palladium/carbon or platinum to the solution, and then performing the reaction at a temperature of from room temperature to 60°C under a hydrogen flow or under pressure. A compound of the formula (VII) can be obtained by allowing a compound of the formula (XIV) to react with 1 to 5 equivalents of a regent such as triethyl orthoformate or triethyl orthoacetate in the absence of a solvent or in the presence of 1 to 5 equivalents of an organic acid such as acetic acid, trifluoroacetic acid or p-toluenesulfonic acid, or an inorganic acid such as hydrochloric acid. The reaction can generally be performed at a temperature of from room temperature to 250°C. The compounds of the formula (A) and the formula (B), useful as synthetic intermediates of the compounds of the formula (I), correspond to the compounds of the formula (XIII) and formula (XIV) wherein X is hydrogen atom, respectively.

〈Preparation Method 3〉

[0048] When A is a group represented by the following formula:



a compound of the following formula (XV) can be prepared by a method similar to Preparation Methods 1 and 2 using a compound of the aforementioned formula (VI) or a compound of the formula (IX).



(XV)

[0049] In the formula, R^1, R^2, R^3, R^4, R^5, and X have the same meanings as those defined above.

[0050] N-oxide compounds can be prepared by oxidizing a starting material by an ordinarily used method.

[0051] When the compounds of present invention are used as active ingredients of the medicaments, the compounds, per se, may be administered, or they may be administered as pharmaceutical compositions which are prepared by using pharmaceutically acceptable additives for pharmaceutical preparations. The composition of the pharmaceutical compositions may be chosen depending on solubility and chemical properties of the aforementioned compounds as active ingredients, as well as administration route and schedule. For example, the composition may be orally administered in the forms of granules, powders, tablets, hard capsules, soft capsules, syrups, emulsions, suspensions, solutions and the like, or intravenously, intramuscularly or subcutaneously administered as injections. The composition may be prepared as powders for injection, and administered as injection prepared just before use.

[0052] For the manufacture of pharmaceutical compositions suitable for oral, enteral, parenteral, or topical administration, organic or inorganic pharmaceutical additives can be used. These additives may be a solid or liquid, and examples include carriers and diluents for pharmaceutical formulations and the like. As excipients used for the manufacture of solid pharmaceutical compositions, for example, lactose, sucrose, starch, talc, cellulose, dextrin and the like can be used. For the manufacture of liquid pharmaceutical compositions for oral administration such as emulsions, syrups, suspensions and solutions, commonly used inactive diluents, for example, water, vegetable oils and the like can be used. The pharmaceutical compositions may contain, for example, wetting agents, suspension aids, sweeteners, aromatics, colorants, preservatives and the like as auxiliaries, as well as inactive diluents. A liquid preparation may be prepared and filled in capsules made of a material that can be disintegrated in body such as gelatin. As solvents or suspending agents used for the manufacture pharmaceutical compositions for parenteral administration such as injections, examples include water, propylene glycol, polyethylene glycol, benzyl alcohol, ethyl oleate, lecitin and the like. Method for preparing the pharmaceutical compositions are not particularly limited, and any methods for preparing formulations available in the art can be utilized.

[0053] The medicaments of the present invention can be used as, for example, antiasthmatic agents for therapeutic and/or preventive treatment of asthma. Doses of the medicaments of the present invention for oral administration are generally 0.01 to 1000 mg (as a weight of an active ingredient), preferably 0.01 to 100 mg, per day for an adult. Prefer-

ably, the aforementioned doses are suitably increased or decreased depending on various conditions including the age, conditions and symptoms of a patient, and the presence or absence of a medicament simultaneously administered and the like. The aforementioned daily dose may be administered once a day or twice or three times a day as divided portions with suitable intervals, or intermittently administered every several days. When the medicaments are used as injections or drip infusions, they are preferably administered continuously or intermittently in a dose of from 0.001 to 100 mg (a weight of an active ingredient) per day for an adult.

Examples

[0054] The present invention will be explained more specifically with reference to examples and test examples. However, the scope of present invention is not limited by the examples and test examples.

Example 1: Synthesis of 2-chloro-4-(3-cyclopentyloxy-4-methoxybenzylamino)-5-nitro-6-methylpyrimidine

[0055] 2,4-Dichloro-5-nitro-6-methylpyrimidine (2.0 g) was dissolved in tetrahydrofuran (14 ml) and added with a solution of 3-cyclopentyloxy-4-methoxybenzylamine (2.25 g) dissolved in tetrahydrofuran (7 ml) with stirring and cooling on a salt-ice bath (-10°C). Then, the mixture was added dropwise with triethylamine (1.4 ml), and stirred for 30 minutes on a salt-ice bath (-10°C). The reaction mixture was further added with saturated brine, and then extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure, and the resulting residue was suspended and washed in a mixed solvent of ether and hexane (50:50) to obtain 3.11 g of the title compound.

1H-NMR ($CDCl_3$) δ ppm: 1.59-1.64 (m, 2H), 1.80- 1.96 (m, 6H), 2.73 (s, 3H), 3.84 (s, 3H), 4.70 (d, 2H, J=5.4Hz), 4.74-4.79 (m, 1H), 6.83-6.91 (m, 3H), 8.36 (bs, 1H)

Example 2: Synthesis of 5-amino-4-(3-cyclopentyloxy-4-methoxybenzylamino)-2-chloro-6-methylpyrimidine

[0056] 2-Chloro-4-(3-cyclopentyloxy-4-methoxybenzyl)-5-nitro-6-methylpyrimidine (2.0 g) was dissolved in tetrahydrofuran (14 ml), and the solution was added with methanol (14 ml) and further added with Raney Nickel (1.8 g) under nitrogen atmosphere. The mixture was stirred at room temperature under hydrogen gas atmosphere for 4.5 hours. After the reaction was completed, the reaction suspension was filtered through Celite under nitrogen atmosphere while washing with methanol. The resulting organic layer was concentrated under reduced pressure, and the residue was recrystallized from ether to obtain 1.65 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ ppm: 1.57-1.66 (m, 2H), 1.78-1.97 (m, 6H), 2.31 (s, 3H), 2.90 (bs, 2H), 3.83 (s, 3H), 4.54 (d, 2H, J=5.4Hz), 4.71-4.77 (m, 1H), 5.30 (bs, 1H), 6.79-6.93 (m, 3H)

Example 3: Synthesis of 2-chloro-9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethylpurine (Compound No. 131 in Table 2)

[0057] 5-Amino-4-(3-cyclopentyloxy-4-methoxybenzyl)-2-chloro-6-methylpyrimidine (20.0 g) was added with triethyl orthoacetate (8.9 g) and acetic acid (3.3 g), and the mixture was heated for 3 hours with stirring under heating at 100°C, while ethanol generated during the reaction was removed from the reaction system. After the reaction was completed, the reaction mixture was cooled to room temperature and diluted by adding methylene chloride. The mixture was washed with saturated aqueous sodium hydrogencarbonate, and then with saturated brine. The organic layer was dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:ethyl acetate = 80:20) to obtain 18.9 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ ppm: 1.59-1.63 (m, 2H), 1.76-1.90 (m, 6H), 2.58 (s, 3H), 2.80 (s, 3H), 3.81 (s, 3H), 4.64-4.68 (m, 1H), 5.28 (s, 2H), 6.70 (dd, 1H, J=8.2, 2.0Hz), 6.78 (d, 1H, J=8.2Hz), 6.88 (d, 1H, J=2.0Hz)

Example 4: Synthesis of 9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethyl-2-[3-(4 pyridyl)propyloxy]purine (Compound No. 100 in Table 2)

[0058] 4-Pyridinepropanol (29.91 g) was dissolved in tetrahydrofuran (560 ml), andt the solution was added with 60% sodium hydride (8.72 g) and stirred at room temperature for 15 minutes. The mixture was added portionwise with 2-chloro-9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethylpurine (59.10 g) and refluxed by heating for 2 hours. The reaction mixture was cooled and concentrated under reduced pressure, and then the mixture was added with water and

extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol = 90:10) to obtain 68.19 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ ppm: 1.54-1.81 (m, 8H), 2.15-2.22 (m, 2H), 2.86 (t, 2H, J=6.9Hz), 3.80 (s, 3H), 4.43 (t, 2H, J=6.9Hz), 4.62-4.64 (m, 1H), 5.23 (s, 2H), 6.67-6.79 (m, 3H), 7.16 (d, 2H, J=6.7Hz), 8.48 (d, 2H, J=6.7Hz)

Example 5: Synthesis of 4-[[9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethylpurin]-2-yl-3-oxypropyl]pyridine N-oxide (Compound No. 120 in Table 2)

[0059] 9-[(3-Cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethyl-2-[3-(4-pyridyl)propoxy] purine (3 g) was dissolved in methylene chloride (30 ml), and the solution was added with MMPP (magnesium monoperoxyphthalate hexahydrate, 3.85 g) dissolved in distilled water (30 ml) with ice cooling, and then the mixture was stirred at room temperature for 3 hours. After complete consumption of the starting material was observed by TLC, the reaction mixture was poured into 5% aqueous solution of sodium sulfate with ice cooling, and the mixture was stirred at room temperature to decompose excessive MMPP. The reaction mixture was extracted with methylene chloride, washed with saturated aqueous sodium hydrogencarbonate, and further washed with saturated brine. The resulting organic layer was dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (chloroform:methanol = 90:10), and the resulting compound was recrystallized from THF-heptane to obtain 2.22 g of the title compound.

^{1}H-NMR ($CDCl_3$) δ ppm: 1.56-1.81 (m, 8H), 2.10-2.19 (m, 2H), 2.51 (s, 3H), 2.75 (s, 3H), 2.85-2.90 (m, 2H), 3.81 (s, 3H), 4.40-4.44 (m, 2H), 4.63-4.64 (m, 1H), 5.24 (s, 2H), 6.65-6.79 (m, 3H), 7.14 (d, 2H, J=6.7Hz), 8.13 (d, 2H, J=6.7Hz)

Example 6: Synthesis of 2-chloro-9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6-methylaminopurine (Compound No. 136 in Table 2)

[0060] 9-[(3-Cyclopentyloxy-4-methoxy)benzyl]-2,6-dichloropurine (8.07 g) was dissolved in tetrahydrofuran (80 ml), added dropwise with methylamine (40% solution in methanol, 8.0 g) with stirring and cooling on an ice bath, and the mixture was stirred at room temperature for 1 hour. The reaction mixture was concentrated under reduced pressure, and the residue was added with water and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure to obtain 7.81 g of the title compound.

Example 7: Synthesis of 9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6-methylamino-2-(3-pyridazinylmethyloxy)purine (Compound No. 79 in Table 2)

[0061] 3-Pyridazinylmethanol (4.41 g) was dissolved in N,N-dimethylformamide (100 ml), added with 60% sodium hydride (1.60 g), and stirred at room temperature for 30 minutes. The reaction mixture was added portionwise with 2-chloro-9-[(3-cyclo-pentyloxy-4-methoxy)benzyl]-6-methylaminopurine (7.76 g), and then the mixture was stirred at 85°C for 2 hours with heating. The reaction mixture was cooled, and concentrated under reduced pressure. The residue was added with water, and extracted with ethyl acetate. The organic layer was washed with saturated brine, dried over anhydrous magnesium sulfate, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain 3.23 g of the title compound.

Example 8

[0062] According to the methods of Examples 1 to 7, compounds shown in Table 2 and Table 3 below were obtained (in the tables, melting points are indicated as °C).

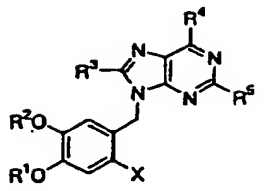


Table 2

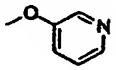
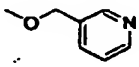
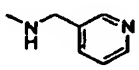
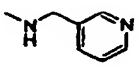
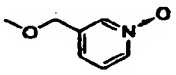
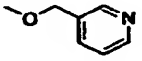
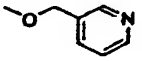
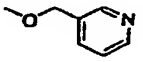
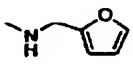
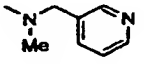
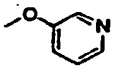
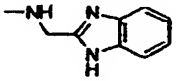
Compound No	X	R1	R2	R3	R4	R5	Physicochemical property
1	H	Me		H		H	amorphous solid
2	H	Me		H		H	oil
3	H	Me		H		H	mp 138-140
4	Br	Me	Me	H		H	mp 185-186
5	H	Me		H		H	mp 76-83
6	Br	Me	Me	H		H	mp 80-82
7	H	Me	Me	H		H	oil
8	H	Me	*i*-Pr	H		H	oil
9	H	Me		H		H	mp 142-144
10	H	Me		H		H	oil
11	Br	Me	Me	H		H	mp 152-154
12	H	Me		H		H	mp 219-223

Table 2 (continued)

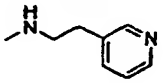
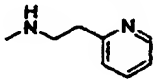
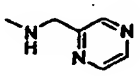
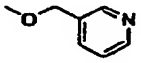
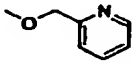
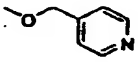
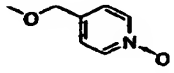
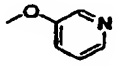
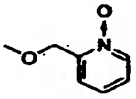
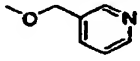
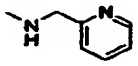
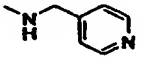
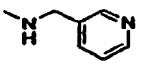
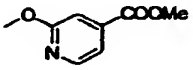
Compound No	X	R1	R2	R3	R4	R5	Physicochemical property
13	H	Me		H		H	mp 113-116
14	H	Me		H		H	oil
15	H	Me		H		H	oil
16	H	Me		H	H		mp 114-115
17	H	Me		H	H		mp 129-130
18	H	Me		H	H		mp 105
19	H	Me		H	H		mp 105-106
20	H	Me		H	H		amorphous solid
21	H	Me		H	H		mp 132
22	H	Me	*i*-Pr	H	H		mp 85-88
23	H	Me		H	H		mp 122-123
24	H	Me		H	H		mp 157-158
25	H	Me		H	H		mp 123-124
26	H	Me		H	H		mp 130-131

Table 2 (continued)

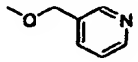
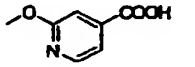
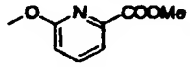
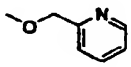
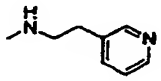
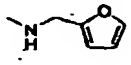
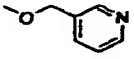
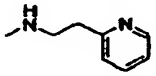
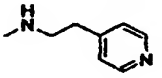
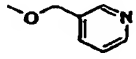
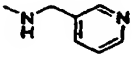
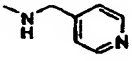
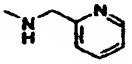
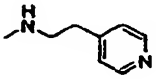
Compound No	X	R1	R2	R3	R4	R5	Physicochemical property
27	H	Me		H	H		mp 114-118
28	H	Me		H	H		amorphous solid
29	H	Me		H	H		mp 122-123
30	H	Me		OH	H		mp 167-169
31	H	Me		H	H		mp 110
32	H	Me		H	H		mp 159
33	H	Me		OH	H		mp 91-93
34	H	Me		H	H		mp 116-117
35	H	Me		H	H		mp 108-109
36	H	Me		Me	H		oil
37	H	Me		Me	H		oil
38	H	Me		Me	H		mp 181-183
39	H	Me		Me	H		mp 77-79
40	H	Me		Me	H		mp 110-112

Table 2 (continued)

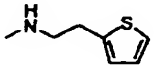
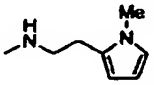
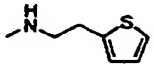
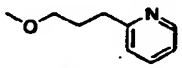
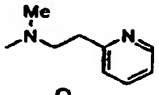
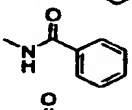
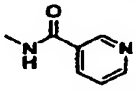
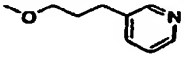
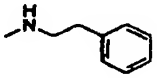
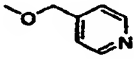
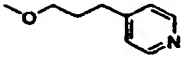
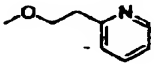
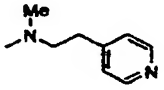
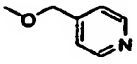
Compound No	X	R1	R2	R3	R4	R5	Physicochemical property
41	H	Me		H	H		mp 141-142
42	H	Me		H	H		mp 120-121
43	H	Me		H	H		mp 112-113
44	H	Me		H	H		oil
45	H	Me		H	H		oil
46	H	Me		H	H		amorphous solid
47	H	Me		H	H		mp 255(dec.)
48	H	Me		H	H		mp 77-78
49	H	Me		H	H		mp 110-111
50	H	Me		Me	H		mp 114-116
51	H	Me		H	H		mp 97-98
52	H	Me		H	H		oil
53	H	Me		H	H		oil
54	H	Me		H	H		mp 116-118

Table 2 (continued)

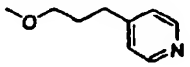
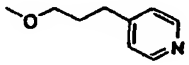
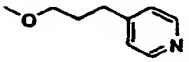
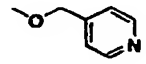
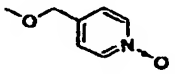
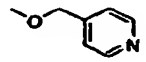
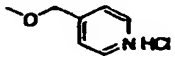
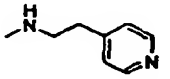
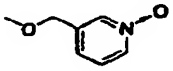
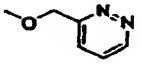
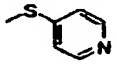
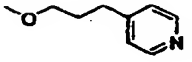
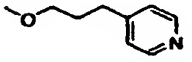
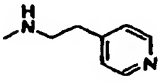
Compound No	X	R1	R2	R3	R4	R5	Physicochemical property
55	H	Me		H	H		mp 128-130
56	H	Me		Me	H		mp 115-117
57	H	Me	*i*-Pr	Me	H		mp 129-132
58	H	Me	*i*-Pr	Me	H		mp 142-144
59	H	Me		Me	H		mp 183-185
60	H	Me		MeO	MeO		amorphous solid
61	H	Me		Me	H		mp 154-156
62	H	Me		Me	H		amorphous solid
63	H	Me		H	H		mp 161-162
64	H	Me		Me	H		mp 82-84
65	H	Me		H	H		mp 216-217
66	H	Me		H	NH_2		mp 152-153
67	H	Me		H	Me		mp 102
68	H	Me		H	MeNH		mp 131-132

Table 2 (continued)

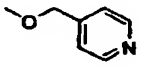
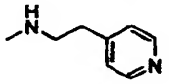
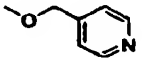
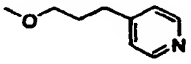
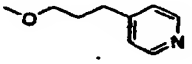
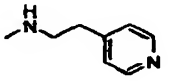
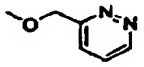
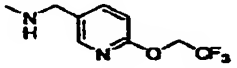
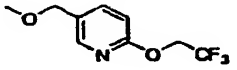
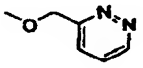
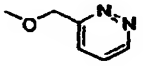
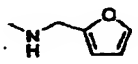
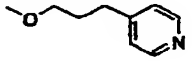
Compound No	X	R1	R2	R3	R4	R5	Physicochemical property
69	H	Me		H	Me		mp 138-139
70	H	Me		H	Me		mp 105-106
71	H	Me		H	MeNH		mp 152-153
72	H	Me		H	MeNH		mp 138-140
73	H	Me		H	MeO		mp 144
74	H	Me		H	MeO		oil
75	H	Me		H	MeO		oil
76	H	Me		H	Me		oil
77	H	Me		Me	H		mp 125-127
78	H	Me		Me	H		mp 99-100
79	H	Me		H	MeNH		mp 176-177
80	H	Me		H	MeO		mp 147-149
81	H	Me		H	Me		mp 141-142
82	H	Me		H	Me_2N		mp 78-80

Table 2 (continued)

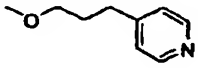
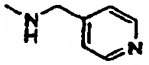
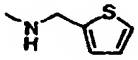
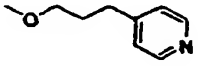
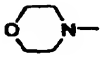
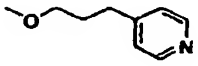
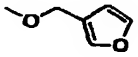
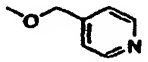
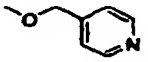
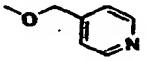
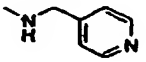
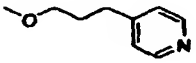
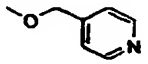
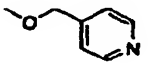
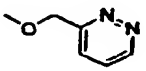
Compound No	X	R1	R2	R3	R4	R5	Physicochemical property
83	H	Me		H	EtNH		mp 127-128
84	H	Me		H	Me		mp 137-138
85	H	Me		H	Me		mp 155
86	H	Me		H			mp 131-132
87	H	Me		H			mp 121
88	H	Me		H	Me_2N		mp 92-93
89	H	Me		H	Me_2N		mp 88-89
90	H	Me		Et	H		mp 134-136
91	H	Me	CF_3CH_2	Me	H		mp 129-130
92	H	Me		H	Et		mp 104-106
93	H	Me		H	*n*-PrNH		mp 130-131
94	H	Me	*n*-Bu	Me	H		mp 94-97
95	H	Me		Me	Me		mp 125-126
96	H	Me		H	EtNH		mp 121-122

Table 2 (continued)

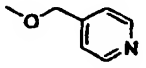
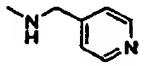
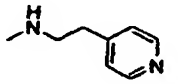
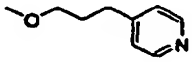
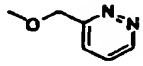
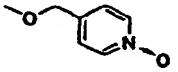
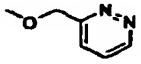
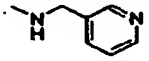
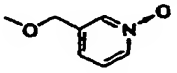
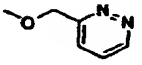
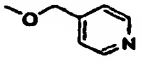
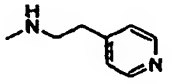
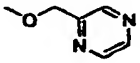
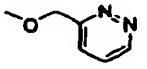
Compound No	X	R1	R2	R3	R4	R5	Physicochemical property
97	H	Me	*t*-Bu	Me	H		mp 162-163
98	H	Me		Me	Me		mp 138-139
99	H	Me		Me	Me		oil
100	H	Me		Me	Me		mp 105-106
101	H	Me		Me	Me		amorphous solid
102	H	Me		Me	Me		mp 157-158
103	H	Me		H	Me_2N		amorphous solid
104	H	Me		H	Me_2N		mp 112-114
105	H	Me		Me	Me		mp 130-131
106	H	Me	*n*-Bu	H	MeNH		mp 165-166
107	H	Me	*n*-Bu	H	Me_2N		mp 105-107
108	H	Me		H	Et		mp 127-129
109	H	Me		Me	Me		oil
110	H	Me		H	NH_2		mp 141-142

Table 2 (continued)

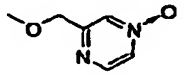
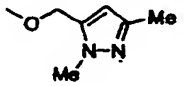
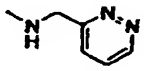
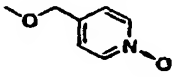
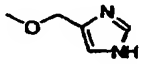
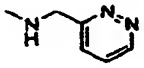
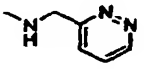
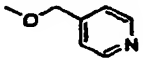
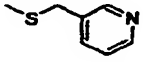
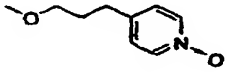
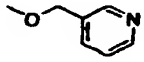
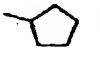
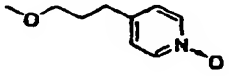
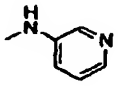
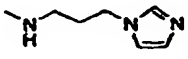
Compound No	X	R1	R2	R3	R4	R5	Physicochemical property
111	H	Me		Me	Me		mp 139-140
112	H	Me		Me	Me		mp 112-123
113	H	Me		Me	Me		mp 164-166
114	H	Me		H	Me		mp 142-143
115	H	Me		Me	Me		amorphous solid
116	H	Me		H	MeNH		mp 149-152
117	H	Me		H	Me		mp 161-163
118	H	Me		H	EtNH		mp 129-130
119	H	Me		Me	Me		mp 116-117
120	H	Me		Me	Me		mp 135-138
121	H	Me		Me	Me		mp 94-95
122	H	Me		H	EtNH		mp 85-88
123	H	Me		H		H	mp 181-183
124	H	Me		H	H		mp 60-61

Table 2 (continued)

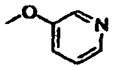
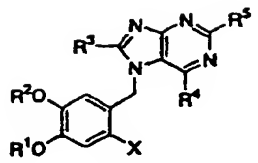
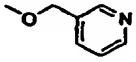
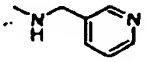
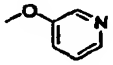
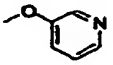
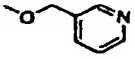
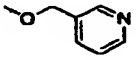
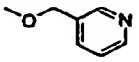
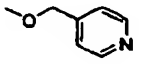
Compound No	X	R1	R2	R3	R4	R5	Physicochemical property
125	H	Me		Cl		Cl	mp 146-149
126	MeO	Me	Me	H	H	H	mp 119-120
127	Br	Me	Me	H	H	H	mp 161-163
128	Br	Me	Me	H	Cl	H	mp 172-173
129	Br	Me		H	H	H	mp 122-124
130	NO_2	Me	Me	H	H	H	mp 184-186
131	H	Me		Me	Me	Cl	mp 120-122
132	H	Me		Me	Me	MeO	oil
133	H	Me		H	Cl	Cl	mp 133-134
134	H	Me		H	NHEt	Cl	mp 129-131
135	H	Me		H	Me	Cl	mp 131-132
136	H	Me		H	NHMe	Cl	mp 155-156

Table 3



Compound No	X	R1	R2	R3	R4	R5	Physicochemical property
137	H	Me		H		H	mp 143-145
138	H	Me		H		H	mp 149-150
139	H	Me		H		H	mp 134-135
140	Br	Me	Me	H		H	mp 172-176
141	H	Me	Me	H		H	mp 137-138
142	H	Me	*i*-Pr	H		H	mp 138-142
143	Br	Me	Me	H	Cl	H	mp 171-174
144	NO_2	Me	Me	H	H	H	mp 162-164
145	Br	Me	Me	H		H	mp 159-161
146	Br	Me		H	H	H	mp 167-169
147	H	Me		Me	H		mp 185-187
148	Br	Me	Me	H	H	H	amorphous solid

[0063] NMR data are shown below for the following compounds (compound numbers are those shown in Tables 2 and 3),.

No.1

[0064]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.51-1.69 (m, 2H), 1.71-1.98 (m, 6H), 3.84 (s, 3H), 4.65-4.75 (m, 1H), 5.37 (s, 2H), 6.79-6.94 (m, 3H), 7.42 (dd, 1H), 7.64-7.72 (m, 1H), 8.02 (s, 1H), 8.53-8.58 (m, 1H), 8.54 (s, 1H), 8.65 (d, 1H)

No.2

[0065]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.50-1.69 (m, 2H), 1.70-1.95 (m, 6H), 3.82 (s, 3H), 4.65-4.73 (m, 1H), 5.32 (s, 2H), 5.70 (s, 2H), 6.78-6.88 (m, 3H), 7.30 (dd, 1H), 7.88 (s, 1H), 7.87-7.94 (m, 1H), 8.55-8.60 (m, 1H), 8.58 (s, 1H), 8.80 (d, 1H)

No. 7

[0066]

^{1}H-NMR ($CDCl_3$) δ ppm: 3.83 (s, 3H), 3.87 (s, 3H), 5.35 (s, 2H), 5.70 (s, 2H), 6.80-6.90 (m, 3H), 7.30 (dd, 1H), 7.89 (s, 1H), 7.87-7.94 (m, 1H), 8.55-8.60 (m, 1H), 8.59 (s, 1H), 8.80 (d, 1H)

No. 8

[0067]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.32 (d, 6H), 3.83 (s, 3H), 4.47 (m, 1H), 5.32 (s, 2H), 5.70 (s, 2H), 6.80-6.90 (m, 3H), 7.30 (dd, 1H) 7.89 (s, 1H), 7.87-7.94 (m, 1H), 8.55-8.60 (m, 1H), 8.58 (s, 1H), 8.80 (d, 1H)

No. 10

[0068]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.5-1.7 (m, 2H), 1.70-1.95 (m, 6H), 3.50 (br, 3H), 3.82 (s, 3H), 4.65-4.75 (m, 1H), 5.28 (s, 2H), 5.40 (br, 2H), 6.75-6.95 (m, 3H), 7.20-7.30 (m, 1H), 7.60-7.70 (m, 1H), 7.70 (s, 1H), 8.43 (s, 1H), 8.51 (m, 1H), 8.59 (s, 1H)

No. 14

[0069]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.59 (m, 2H), 1.81-1.93 (m, 6H), 3.02 (t, 2H), 3.83 (s, 3H), 3.97 (m, 2H), 4.68-4.71 (m, 1H), 5.27 (s, 2H), 5.84 (m, 1H), 6.80-6.90 (m, 3H), 7.20 (d, 2H), 7.68 (s, 1H), 8.45 (s, 1H), 8.52 (d, 2H)

No. 15

[0070]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.50-1.70 (m, 2H), 1.70-1.95 (m, 6H), 3.83 (s, 3H), 4.65-4.73 (m, H), 5.34 (s, 2H), 5.84 (s, 2H), 6.80-6.95 (m, 3H), 7.91 (s, 1H), 8.50-8.60 (m, 3H), 8.85 (s, 1H)

No. 20

[0071]

1H-NMR ($CDCl_3$) δ ppm: 1.58-1.60 (m, 2H), 1.80-1.87 (m, 6H), 3.83 (s, 3H), 4.65-4.75 (m, 1H), 5.22 (s, 2H), 6.83-6.84 (m, 3H), 7.39 (dd, 1H), 7.60 (ddd, 1H), 7.94 (s, 1H), 8.52 (dd, 1H), 8.62 (d, 1H), 8.89 (s, 1H)

No. 28

[0072]

^{1}H-NMR (DMSO-d_6) δ ppm: 1.51-1.77 (m, 8H), 3.70 (s, 3H), 4.44 (s, 2H), 4.68 (m, 1H), 6.50 (d, 1H), 6.86-6.93 (m, 4H), 7.84 (s, 1H), 8.33 (s, 2H)

No. 36

[0073]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.53-1.61 (m, 2H), 1.70-1.81 (m, 6H), 2.52 (s, 3H), 3.81 (s, 3H), 4.61-4.65 (m, 1H), 5.27 (s, 2H), 5.52 (s, 2H), 6.66-6.84 (m, 3H), 7.27-7.32 (m, 1H), 7.84-7.88 (m, 1H), 8.53-8.60 (m, 1H), 8.74-8.77 (m, 2H)

No. 37

[0074]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.53-1.59 (m, 2H), 1.75-1.90 (m, 6H), 2.46 (s, 3H), 3.81 (s, 3H), 4.59-4.63 (m, 1H), 4.68 (d, 2H, J=6.0Hz) 5.15 (m, 2H), 6.15-6.25 (m, 1H), 6.62-6.78 (m, 3H), 7.19 (dd, 1H, J=4.6, 7.8Hz), 7.70 (ddd, 1H, J=1.9, 1.9, 7.8Hz), 8.45 (dd, 1H, J=1.9, 4.6Hz), 8.53 (s, 1H), 8.63(d, 1H, J=1.9Hz)

No. 44

[0075]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.56-1.59 (m, 2H), 1.80-1.84 (m, 6H), 2.30-2.35 (m, 2H), 3.04 (t, 2H), 3.82 (s, 3H), 4.52 (t, 2H), 4.68-4.70 (m, 1H), 5.26 (s, 2H), 6.81-6.88 (m, 3H), 7.10-7.13 (m, 1H), 7.20 (d, 1H), 7.58 (m, 1H), 7.86 (s, 1H), 8.54 (dd, 1H), 8.86 (s, 1H)

No. 45

[0076]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.54-1.56 (m, 2H), 1.80-1.81 (m, 6H), 3.15 (t, 2H), 3.17 (s, 3H), 3.81 (s, 3H), 4.08 (t, 2H), 4.68 (m, 1H), 5.17 (s, 2H), 6.79-6.89 (m, 3H), 7.10-7.16 (m, 2H), 7.55 (m, 1H), 7.67 (s, 1H), 8.55 (d, 1H), 8.73 (s, 1H)

No. 46

[0077]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.48-1.65 (m, 2H), 6.93 (dd, 1H), 8.99 (s, 1H), 1.68-1.98 (m, 6H), 7.00 (d, 1H), 3.83 (s, 3H), 4.70-4.80 (m, 1H), 5.34 (s, 2H), 6.84 (d, 1H), 7.48-7.64 (m, 3H), 7.94 (s, 1H), 7.94-8.01 (m, 2H), 8.79 (brs, 1H)

No. 52

[0078]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.55-1.58 (m, 2H), 1.76-1.83 (m, 6H), 3.36 (t, 2H), 3.82 (s, 3H), 4.68-4.70 (m, 1H), 4.85 (t, 2H), 5.25 (s, 2H), 6.80-6.87 (m, 3H), 7.12-7.16 (m, 1H), 7.31 (d, 1H), 7.62 (ddd, 1H), 7.84 (s, 1H), 8.56 (d, 1H), 8.86 (s, 1H)

No. 53

[0079]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.56 (m, 2H), 1.81 (m, 6H), 2.95 (t, 2H), 3.18 (s, 3H), 3.81 (s, 3H), 3.94 (t, 2H), 4.68 (m,

1H), 5.18 (s, 2H), 6.80-6.87 (m, 3H), 7.16 (d, 2H), 7.67 (s, 1H), 8.49 (d, 2H), 8.74 (s, 1H)

No. 60

[0080]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.47- 1.67 (m, 2H), 1.71-2.01 (m, 6H), 3.80 (s, 3H), 4.09 (s, 3H), 4.17 (s, 3H), 4.63-4.75 (m, 1H), 5.03 (s, 2H), 5.47 (s, 2H), 6.70 (d, 1H), 6.75 (dd, 1H), 6.93 (d, 1H), 7.38 (d, 2H), 8.59 (d, 2H)

No. 62

[0081]

^{1}H-NMR ($CDCl_3$) δ ppm: 2.00-2.15 (m, 2H), 2.46 (s, 3H), 2.96 (t, 2H), 3.70-4.03 (m, 6H), 3.82 (s, 3H), 4.78-4.85 (m, 1H), 5.19 (s, 2H), 5.20 (brs, 1H), 6.70-6.85 (m, 3H), 7.17 (d, 2H), 8.51 (d, 2H), 8.57 (s, 1H)

No. 74

[0082]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.56-1.58 (m, 2H), 1.76-1.84 (m, 6H), 2.17-2.22 (m, 2H), 2.85 (t, 2H), 3.82 (s, 3H), 4.16 (s, 3H), 4.45 (t, 2H), 4.67-4.68 (m, 1H), 5.20 (s, 2H), 6.81-6.82 (m, 3H), 7.16 (d, 2H), 7.68 (s, 1H), 8.50 (d, 2H)

No. 75

[0083]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.56 (m, 2H), 1.81 (m, 6H), 2.96 (t, 2H), 3.74 (q, 2H), 3.81 (s, 3H), 4.07 (s, 3H), 4.66-4.68 (m, 1H) 5.07 (t, 1H), 5.15 (s, 2H), 6.81 (m, 3H), 7.16 (d, 2H), 7.54 (s, 1H), 8.52 (d, 2H)

No. 76

[0084]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.59 (m, 2H), 1.80-1.83 (m, 6H), 2.79 (s, 3H), 3.83 (s, 3H), 4.70 (m, 1H), 5.22 (s, 2H), 5.88 (s, 2H), 6.82 (m, 3H), 7.48 (dd, 1H), 7.79 (d, 2H), 7.83 (s, 1H), 9.15 (d, 1H)

No. 99

[0085]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.50-1.85 (m, 8H), 2.46-2.52 (m, 3H), 2.63-2.75 (m, 3H), 2.88-2.97 (m, 2H), 3.54-3.58 (m, 2H), 3.81 (s, 3H), 4.54-4.58 (m, 1H), 4.63 (brs, 1H), 5.16-5.24 (m, 2H), 6.67-6.79 (m, 3H), 7.14-7.18 (m, 2H), 8.49-8.52 (m, 2H)

No. 101

[0086]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.50-1.60 (m, 2H), 1.75-1.90 (m, 6H), 2.54 (s, 3H), 2.76 (s, 3H), 3.81 (s, 3H), 4.60-4.70 (m, 1H), 5.23 (s, 2H), 5.86 (s, 2H), 6.64-6.78 (m, 3H), 7.48 (dd, 1H, J=4.9, 8.5 Hz), 7.79 (dd, 1H, J=1.5, 8.5Hz), 9.14 (dd, 1H, J=1.5, 4.9 Hz)

No. 103

[0087]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.50-1.64 (m, 2H), 5.81 (s, 2H), 1.70-1.94 (m, 6H), 6.70-6.90 (m, 3H), 3.40 (brs, 6H), 3.82

(s, 3H), 4.64-4.72 (m, 1H), 5.15 (s, 2H), 7.44 (dd, 1H), 7.53 (s, 1H), 7.72 (dd, 1H), 9.11 (dd, 1H)

No. 109

[0088]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.50-1.60 (m, 2H), 1.70-1.90 (m, 6H), 2.52 (s, 3H), 2.76 (s, 3H), 3.81 (s, 3H), 4.60-4.70 (m, 1H), 5.22 (s, 2H), 5.66 (s, 2H), 6.63-6.83 (m, 3H), 8.52-8.55 (m, 2H), 8.86 (s, 1H)

No. 115

[0089]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.50-1.60 (m, 2H), 1.60-1.90 (m, 6H), 2.59 (s, 3H), 2.82 (s, 3H), 3.81 (s, 3H), 4.60-4.65 (m, 2H), 4.69 (s, 1H), 5.31 (s, 2H), 6.72-6.82 (m, 3H), 7.94 (d, 1H, J=1.2Hz), 8.65 (d, 1H, J=1.2Hz)

No. 120

[0090]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.56-1.81 (m, 8H), 2.10-2.19 (m, 2H), 2.51 (s, 3H), 2.75 (s, 3H), 2.85-2.90 (m, 2H), 3.81 (s, 3H), 4.40-4.44 (m, 2H), 4.63-4.64 (m, 1H), 5.24 (s, 2H), 6.65-6.79 (m, 3H), 7.14 (d, 2H, J=6.7Hz), 8.13 (d, 2H, J=6.7Hz)

No. 132

[0091]

^{1}H-NMR ($CDCl_3$) δ ppm: 1.50-1.90 (m, 8H), 2.52 (s, 3H), 2.74 (s, 3H), 3.81 (s, 3H), 4.05 (s, 3H), 4.62-4.64 (m, 1H), 5.25 (s, 3H), 6.70-6.79 (m, 3H)

No. 148

[0092]

^{1}H-NMR ($CDCl_3$) δ ppm: 3.80 (s, 3H), 3.90 (s, 3H), 5.46 (s, 2H), 6.72 (s, 1H), 7.10 (s, 1H), 8.29 (s, 1H), 8.85 (s, 1H), 9.15 (s, 1H)

Example 9: Manufacture of tablets

[0093] Well pulverized 9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethyl-2-[3-(4 pyridyl)propyloxy]purine (Compound No. 100 in Table 2, 1000 g), lactose (5900 g), crystalline cellulose (2000 g), low substituted hydroxypropylcellulose (1000 g) and magnesium stearate (100 g) were well mixed, and made into plain tablets containing 10 mg of the compound per one tablet of 100 mg by the direct compression method. These plain tablet were subjected to sugar coatings or film coatings to prepare sugar-coated tablets and film-coated tablets.

Example 10: Manufacture of capsules

[0094] Well-pulverized 9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6-methylamino-2-[(3-pyridazinyl)methyloxy]purine (Compound No. 79 in Table 2, 1000 g), corn starch (3000 g), lactose (6900 g), crystalline cellulose (1000 g) and magnesium stearate (100 g) were mixed to prepare capsules containing 10 mg of the compound per each 120 mg capsule.

Example 11: Production of inhalant

[0095] Well-pulverized 9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6-ethylamino-2-[(3 pyridazinyl)methyloxy]purine (Compound No. 96 in Table 2, 5 g), medium chain saturated fatty acid triglyceride (10 g) and sorbitan monooleate (0.2 g) were well mixed, and 15.2 mg of the mixture was weighed and placed in a 5-ml aluminum container for aerosol. 84.8 mg of Freon 12/114 (1:1 mixture) was charged at a low temperature into the container, and the container was equipped

with a constant volume adapter of 10.0 μl per one spraying to obtain an inhalant for constant volume spraying containing 5 mg of the compound per one container of 5 ml.

Test Example

[0096] PDE IV inhibitory activity of the compounds of the present invention was examined. Rolipram used as control is a compound disclosed in Japanese Patent Unexamined Publication (Kokai) No. 50-157360/1975, of which structure is shown in the section of related art of the present specification. Adv. Second Messenger Phosphoprotein Res., 22, 1, (1988) and other articles disclose that this compound has specific inhibitory activity against PDE IV.

Test Example 1: Effect on enzymatic activity of type IV phosphodiesterase (PDE IV)

[0097] The crude enzyme was purified from a cytoplasmic fraction of human monocyte-like cell strain U937 by using a Q-Sepharose column according to the method of Nicholson et al. [Br. J. Pharmacol., 97, 889 (1989)]. The enzymatic activity was determined by performing a reaction using 0.4 mM ^{3}H-cAMP as the substrate in 50 mM Tris buffer (pH 8.0) containing 0.1 mg/ml BSA, 1 ml of EDTA and 5 mM $MgCl_2$ at 30°C for 15 minutes, and then separating the produced ^{3}H-5'-AMP using a cation exchange column and measuring its radioactivity according to the method of Hidaka et al. [Biochem. Med., 10, 301 (1974)]. After a test compound was added, the reaction mixture was incubated at 30°C for 15 minutes, and then added with the substrate. Inhibitory ratio at each concentration was obtained based on the reaction performed with no addition of a test compound which was taken as 100%, and a concentration for 50% inhibition (IC_{50}) was calculated by the plot analysis. The results are shown in Table 4.

Table 4

Compound No.	PDE IV Inhibitory Activity: IC^{50} (M)
2	8.9×10^{-9}
32	1.2×10^{-9}
36	2.6×10^{-9}
37	1.0×10^{-9}
39	1.4×10^{-9}

41	4.7×10^{-10}
55	4.5×10^{-9}
56	1.3×10^{-9}
57	4.6×10^{-9}
66	1.4×10^{-9}
72	7.5×10^{-10}
77	8.3×10^{-10}
78	1.3×10^{-9}
79	4.7×10^{-9}
81	3.5×10^{-10}
82	8.2×10^{-10}
83	6.9×10^{-10}
84	1.9×10^{-9}
85	1.3×10^{-10}
88	2.0×10^{-10}
93	4.4×10^{-10}
95	1.7×10^{-9}
96	3.8×10^{-9}
98	1.0×10^{-9}
100	5.5×10^{-10}
101	6.1×10^{-9}
102	1.5×10^{-8}
104	1.1×10^{-9}
112	2.2×10^{-10}
113	2.4×10^{-8}
119	6.4×10^{-10}
120	2.0×10^{-9}
122	1.5×10^{-8}
131	6.7×10^{-9}

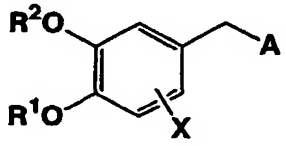
134	4.1×10^{-8}
136	7.4×10^{-8}
137	6.4×10^{-8}
139	5.4×10^{-8}
Rolipram	3.0×10^{-7}

Industrial Applicability

[0098] The compounds of the present invention represented by the formula (I) have excellent PDE IV inhibitory activity, and are useful as active ingredients of medicaments for therapeutic and/or preventive treatment of asthma and the like. The compounds represented by the formulas (A) and (B) are useful as synthetic intermediates for preparation of the compounds represented by the aforementioned formula (I).

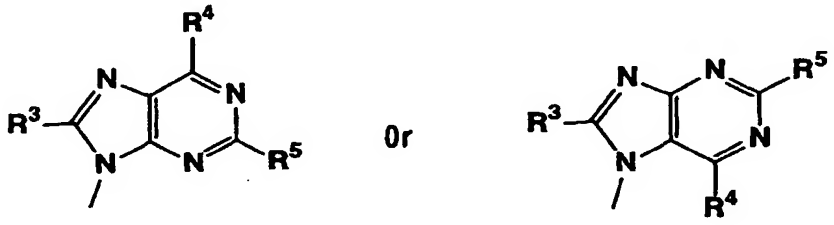
Claims

1. A purine derivative represented by the following formula (I), a salt thereof, or an N-oxide thereof, or a hydrate thereof or a solvate thereof:



(I)

wherein R^1 represents a C_1-C_4 alkyl group or difluoromethyl group; R^2 represents tetrahydrofuranyl group, a C_1-C_7 alkyl group, a C_1-C_7 haloalkyl group, a C_2-C_7 alkenyl group, bicyclo[2,2,1]hept-2-yl group, or a C_3-C_8 cycloalkyl group; X represents hydrogen atom, a halogen atom, or nitro group; and A represents a group represented by the following formula:

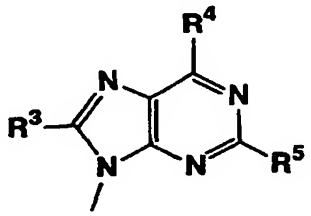


wherein R^3 represents hydrogen atom, a halogen atom, hydroxyl group, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, amino group, a C_1-C_4 alkylamino group, or a C_2-C_8 dialkylamino group; R^4 and R^5 each independently represent hydrogen atom, a halogen atom, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, amino group, a C_1-C_4 alkylamino group, pyrrolidinyl group, morpholino group, a C_2-C_8 dialkylamino group, or a group represented by -Y-$(CH_2)_n$-B {Y

represents -O-, -S-, -NHCO-, or -N(R^6)- (R^6 represents hydrogen atom or a C_1-C_4 alkyl group), n represents an integer of from 0 to 4, and B represents a phenyl group, a naphthyl group, or a heterocyclic residue, each of which may be substituted},
provided that either R^4 or R^5 represents -Y-$(CH_2)_n$-B {Y represents -O-, -S-, -NHCO-, or -N(R^6)- (R^6 represents hydrogen atom or a C_1-C_4 alkyl group)} when X represents hydrogen atom,, and

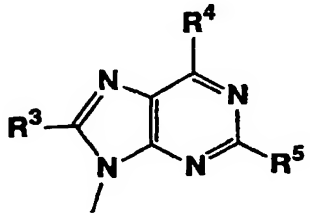
(i) n represents an integer of from 0 to 4, and B represents a phenyl group, a naphthyl group, or a heterocyclic residue, each of which may be substituted when Y represents -O-, -S-, or -NHCO-, or
(ii) n represents an integer of from 1 to 4, and B represents a heterocyclic residue when Y represents -N(R^6)-.

2. The purine derivative, a salt thereof, or an N-oxide thereof, or a hydrate thereof or a solvate thereof according to claim 1, wherein A is a group represented by the following formula:



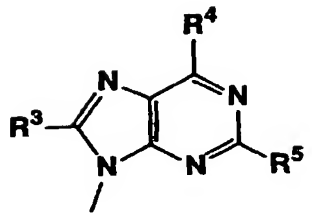
wherein R^3 is hydrogen atom, a halogen atom, hydroxyl group, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, amino group, a C_1-C_4 alkylamino group, or a C_2-C_8 dialkylamino group; one of R^4 and R^5 is hydrogen atom, a halogen atom, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, amino group, a C_1-C_4 alkylamino group, pyrrolidinyl group, morpholino group, or a C_2-C_8 dialkylamino group, and the other is - Y-$(CH_2)_n$-B (Y is -O-, -S-, -NHCO-, or -N(R^6)- (R^6 represents hydrogen atom or a C_1-C_4 alkyl group), n is an integer of from 0 to 4, and B represents a phenyl group, a naphthyl group or a heterocyclic residue, each of which may be substituted.

3. The purine derivative, a salt thereof, or an N-oxide thereof, or a hydrate thereof or a solvate thereof according to claim 1, wherein R^1 is a C_1-C_4 alkyl group; R^2 is tetrahydrofuranyl group, a C_1-C_6 alkyl group, a C_1-C_3 haloalkyl group, or a C_3-C_8 cycloalkyl group, and A is a group represented by the following formula:



wherein R^3 is hydrogen atom, a halogen atom, hydroxyl group, a C_1-C_4 alkyl group or a C_1-C_4 alkoxyl group; R_4 is hydrogen atom, a halogen atom, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, a C_1-C_4 alkylamino group, or a C_2-C_8 dialkylamino group, R^5 is -Y-$(CH_2)_n$-B (Y is -O-, -S-, or -NHCO-, n is an integer of from 1 to 4, and B represents a heterocyclic residue which may be substituted).

4. The purine derivative, a salt thereof, or an N-oxide thereof, or a hydrate thereof or a solvate thereof according to claim 1, wherein R^1 is a C_1-C_3 alkyl group; R^2 is a C_3-C_8 cycloalkyl group, and A is a group represented by the following formula:



wherein R^3 is hydrogen atom, a C_1-C_3 alkyl group or a C_1-C_3 alkoxyl group; R^4 is a C_1-C_3 alkyl group, a C_1-C_3 alkoxyl group or a C_1-C_3 alkylamino group; R^5 is -Y-$(CH_2)_n$-B (Y is -O-, n is an integer of from 1 to 4, and B is a heterocyclic residue which may be substituted).

5. 2-Chloro-9-[(3-cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethy]purine or a salt thereof, or a hydrate thereof or a solvate thereof.

6. 9-[(3-Cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethyl-2-methoxypurine or a salt thereof, or a hydrate thereof or a solvate thereof.

7. 9-[(3-Cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethyl-2-(pyridazinylmethyloxy)purine or a salt thereof, or a hydrate thereof or a solvate thereof.

8. 9-[(3-Cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethyl-2-[4-pyridylmethyloxy]purine or a salt thereof, or a hydrate thereof or a solvate thereof.

9. 4-[[9-[(3-Cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethylpurin]-2-yl-oxymethyl]pyridine N-oxide or a salt thereof, or a hydrate thereof or a solvate thereof.

10. 9-[(3-Cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethyl-2-[2-(4-pyridyl)ethyloxy]purine or a salt thereof, or a hydrate thereof or a solvate thereof.

11. 4-[[9-[(3-Cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethylpurin]-2-yl-2-oxyethyl]pyridine N-oxide or a salt thereof, or a hydrate thereof or a solvate thereof.

12. 9-[(3-Cyclopentyloxy-4-methoxy)benzyl]-6-methylamino-2-(3-pyridazinylmethyloxy)purine or a salt thereof, or a hydrate or a solvate thereof.

13. 9-[(3-Cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethyl-2-[2-(4-pyridyl)ethylamino]purine or a salt thereof, or a hydrate thereof or a solvate thereof.

14. 9-[(3-Cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethyl-2-[(4-pyridyl)methylamino]purine or a salt thereof, or a hydrate thereof or a solvate thereof.

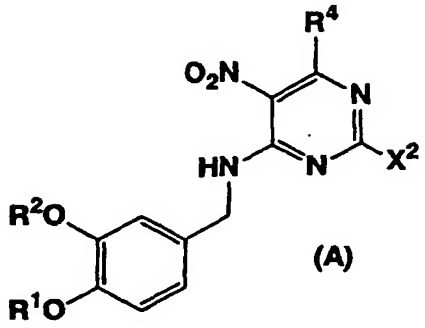
15. 9-[(3-Cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethyl-2-[3-(4-pyridyl)propyloxy]purine or a salt thereof, or a hydrate thereof or a solvate thereof.

16. 4-[[9-[(3-Cyclopentyloxy-4-methoxy)benzyl]-6,8-dimethylpurin]-2-yl-3-oxypropyl]pyridine N-oxide or a salt thereof, or a hydrate thereof or a solvate thereof.

17. A medicament which comprises a substance selected from the group consisting of the purine derivative, a salt thereof, and an N-oxide compound thereof, and a hydrate thereof and a solvate thereof according to any one of claims 1 to 16 as an active ingredient.

18. The medicament according to claim 17 which is an antiasthmatic agent.

19. A compound represented by the following formula (A):

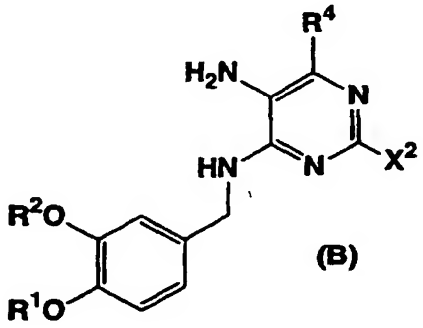


(A)

wherein R^1 represents a C_1-C_4 alkyl group or difluoromethyl group; R^2 represents tetrahydrofuranyl group, a C_1-C_7 alkyl group, a C_1-C_7 haloalkyl group, a C_2-C_7 alkenyl group, bicyclo[2,2,1]hept-2-yl group, or a C_3-C_8 cycloalkyl group; R^4 represents hydrogen atom, a halogen atom, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, amino group, a C_1-C_4 alkylamino group, pyrrolidinyl group, morpholino group, a C_2-C_8 dialkylamino group, or -Y-$(CH_2)_n$-B {Y represents -O-, -S-, -NHCO-, or -N(R^6)- (R^6 represents hydrogen atom or a C_1-C_4 alkyl group), n represents an integer of from 0 to 4, B represents a phenyl group, a naphthyl group, or a heterocyclic residue, each of which may be substituted, and X^2 represents a halogen atom.

20. The compound according to claim 19, wherein R^1 is a C_1-C_4 alkyl group, R^2 is tetrahydrofuranyl group, a C_1-C_6 alkyl group, a C_1-C_3 haloalkyl group, or a C_3-C_8 cycloalkyl group, R^4 is hydrogen atom, a halogen atom, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, a C_1-C_4 alkylamino group, or a C_2-C_8 dialkylamino group.

21. A compound represented by the following formula (B):



(B)

wherein R^1 represents a C_1-C_4 alkyl group or difluoromethyl group; R^2 represents tetrahydrofuranyl group, a C_1-C_7 alkyl group, a C_1-C_7 haloalkyl group, a C_2-C_7 alkenyl group, bicyclo[2,2,1]hept-2-yl group, or a C_3-C_8 cycloalkyl group; R^4 represents hydrogen atom, a halogen atom, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, amino group, a C_1-C_4 alkylamino group, pyrrolidinyl group, morpholino group, a C_2-C_8 dialkylamino group, or -Y-$(CH_2)_n$-B {Y represents -O-, -S-, -NHCO-, or -N(R^6)- (R^6 represents hydrogen atom or a C_1-C_4 alkyl group), n represents an integer of from 0 to 4, B represents a phenyl group, a naphthyl group, or a heterocyclic residue, each of which may be substituted, and X^2 represents a halogen atom.

22. The compound according to claim 21, wherein R^1 is a C_1-C_4 alkyl group, R^2 is tetrahydrofuranyl group, a C_1-C_6 alkyl group, a C_1-C_3 haloalkyl group, or a C_3-C_8 cycloalkyl group, R^4 is hydrogen atom, a halogen atom, a C_1-C_4 alkyl group, a C_1-C_4 alkoxyl group, a C_1-C_4 alkylamino group, or a C_2-C_8 dialkylamino group.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/05092

A. CLASSIFICATION OF SUBJECT MATTER
Int.Cl[6] C07D473/00, C07D473/06, C07D473/16, C07D473/18, C07D473/28, C07D473/32, C07D473/34, 361, C07D473/40, C07D239/48, C07D239/50,
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int.Cl[6] C07D473/00-473/40, C07D239/48, C07D239/50, A61K31/52, A61K31/535

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAplus (STN), REGISTRY (STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, 3862189, A (Warner-Lambert Company), 21 Jan. 1975 (21. 01. 75) (Family: none)	1-17, 19-22
A	US, 3936454, A (Warner-Lambert Company), 3 Feb. 1976 (03. 02. 76) (Family: none)	1-17, 19-22
A	JP, 8-231545, A (Bayer AG.), 10 September, 1996 (10. 09. 96) & EP, 722944, A1 & DE, 19501482, A1 & FI, 9600225, A & CA, 2167353, A & CN, 1135485, A	1-22

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 February, 1999 (01. 02. 99)	9 February, 1999 (09. 02. 99)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP98/05092

A. (Continuation) CLASSIFICATION OF SUBJECT MATTER

A61K31/52, A61K31/535

Form PCT/ISA/210 (extra sheet) (July 1992)